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THE WESTERN Journal of Medicine

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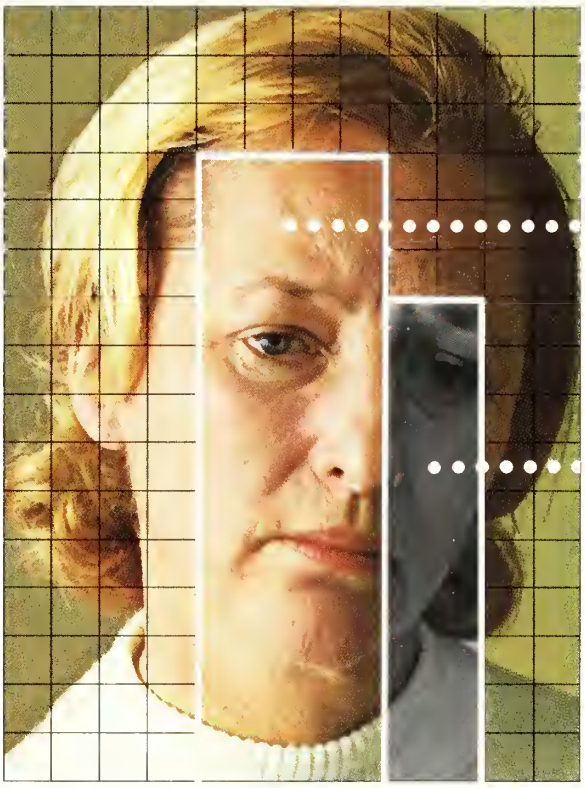


Predominant psychoneurotic anxiety

Associated depressive symptoms

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Tension and anxiety states; somatic complaints which are concomitants of emotional factors; psychoneurotic states manifested by tension, anxiety, apprehension, fatigue, depressive symptoms or agitation; symptomatic relief of acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in skeletal muscle spasm due to reflex spasm to local pathology, spasticity caused by upper motor neuron disorders, athetosis, stiff-man syndrome, convulsive disorders (not for sole therapy).

Contraindicated: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms (similar to those with barbiturates and alcohol) have occurred following abrupt discontinuance (convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Keep addiction-prone individuals under careful

respond to one

According to her major symptoms, she is a psychoneurotic patient with severe anxiety. But according to the description she gives of her feelings, part of the problem may sound like depression. This is because her problem, although primarily one of excessive anxiety, is often accompanied by depressive symptomatology. Valium (diazepam) can provide relief for both—as the excessive anxiety is relieved, the depressive symptoms associated with it are also often relieved.

There are other advantages in using Valium for the management of psychoneurotic anxiety with secondary depressive symptoms: the psychotherapeutic effect of Valium is pronounced and rapid. This means that improvement is usually apparent in the patient within a few days rather than in a week or two, although it may take longer in some patients. In addition, Valium (diazepam) is generally well tolerated; as with most CNS-acting agents, caution patients against hazardous occupations requiring complete mental alertness.

Also, because the psychoneurotic patient's symptoms are often intensified at bedtime, Valium can offer an additional benefit. An *h.s.* dose added to the *b.i.d.* or *t.i.d.* treatment regimen can relieve the excessive anxiety and associated depressive symptoms and thus encourage a more restful night's sleep.

Valium®
(diazepam)
2-mg, 5-mg, 10-mg tablets

in psychoneurotic
anxiety states
with associated
depressive symptoms

surveillance because of their predisposition to habituation and dependence. In pregnancy, lactation or women of childbearing age, weigh potential benefit against possible hazard.

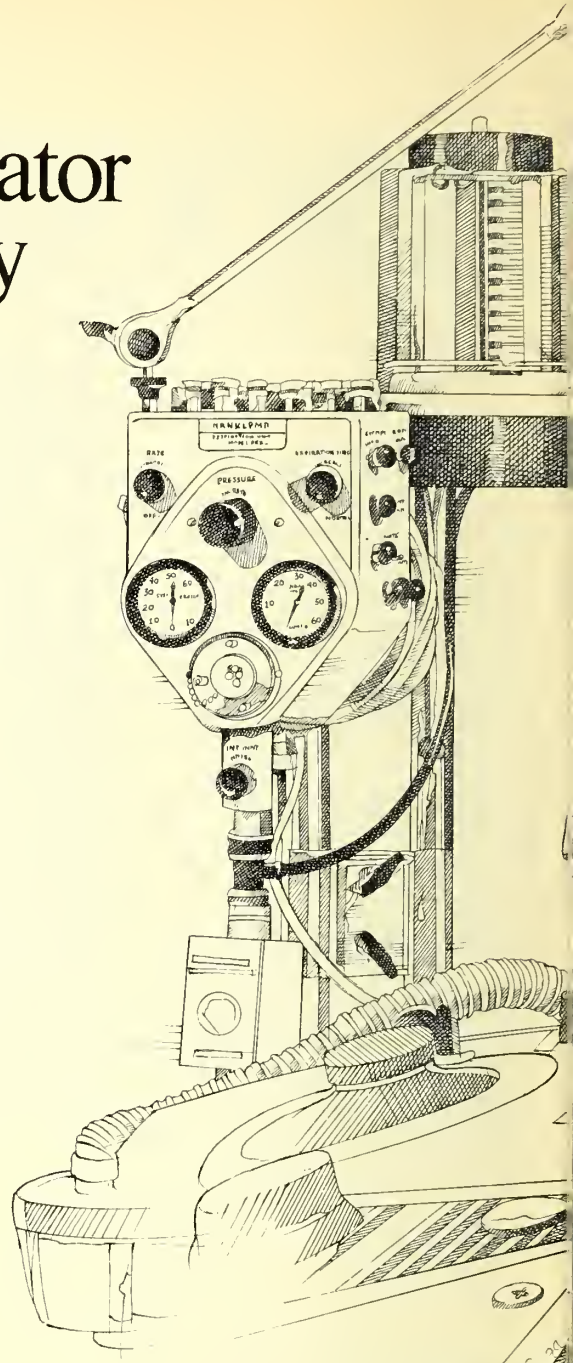
Precautions: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed; drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.

ROCHE

Roche Laboratories
Division of Hoffmann-La Roche Inc.
Nutley, New Jersey 07110

Isoetharine–
The unique bronchodilator with preferential affinity for Beta$_2$ receptors



All sympathomimetic bronchodilators work on Beta adrenergic receptors. However, there are two kinds of Beta receptors—Beta$_1$ that stimulates the heart, Beta$_2$ that dilates the bronchioles. Isoetharine, the bronchodilator used in Bronkosol and Bronkometer, acts preferentially on Beta$_2$ receptors. It has little affinity for cardio-stimulating receptors. For this reason Bronkosol and Bronkometer can open small airways, shrink swollen bronchial mucosa, improve respiratory function and vital capacity. All with minimal direct cardiotonic effect.

Relative effects on Adrenergic Receptors*

Drug and Receptor Selection	Alpha Produces Vasopressor Effects	Beta$_1$ Stimulates Heart	Beta$_2$ Dilates and Relaxes Bronchi and Arterioles
Epinephrine	+++	++++	++
R-epinephrine	++	++	+++
Isoproterenol		++++	+++++
Isoetharine		+	+++

*Ziment, I.: Resp. Therap. 4:51, May-June, 1974.

Bronkometer®

Each ml. of solution delivers approximately 20 metered doses of 56 mg., each containing 340 mcg. isoetharine mesylate (0.61% W/W) and 70 mcg. phenylephrine HCl (0.125% W/W), with saccharin, menthol, alcohol 30% (W/W) and fluorochlorohydrocarbons as gaseous propellants. Preserved with ascorbic acid 0.1% W/W.

Bronkosol®

Isoetharine HCl 1.0%; phenylephrine HCl 0.25%; in an aqueous-glycerin solution containing saccharin sodium with sodium chloride, sodium citrate, sodium bisulfite 0.3%, methylparaben 0.025%, and propylparaben 0.014% as preservatives.

As originally marketed, Bronkometer and Bronkosol contained thenyldiamine hydrochloride. The present formulations have been revised to delete that ingredient.

Indications: Based on a review of Bronkosol and Bronkometer by the National Academy of Sciences — National Research Council and/or other information, FDA has classified the indications as follows:

"Probably" effective for the acute relief of bronchial asthma and other conditions in which bronchospasm is a complicating factor, such as chronic bronchitis or emphysema. Final classification of less-than-effective indications requires further investigation.

Contraindication: Hypersensitivity to any ingredient.

Warnings: Excessive use of an adrenergic aerosol should be discouraged as it may lose effectiveness. Occasional patients have been reported to develop severe paradoxical airway resistance with repeated excessive use of an aerosol adrenergic inhalation preparation. In such instances the use of the aerosol adrenergic should be discontinued immediately and alternative therapy instituted. Cardiac arrest has been noted in several instances.

Should not be administered along with epinephrine or other sympathomimetic amines, since these drugs are direct cardiac stimulants and may cause excessive tachycardia. They may, however, be alternated if desired.

Use in Pregnancy: Although there has been no evidence of teratogenic effects with these drugs, use of any drug in pregnancy, lactation, or in women of childbearing potential requires that the potential benefit of the drug be weighed against its possible hazard to the mother or child.

Precautions: Dosage must be carefully adjusted in patients with hyperthyroidism, hypertension, acute coronary disease, cardiac asthma, limited cardiac reserve, and in individuals sensitive to

with minimal direct cardiotonic action

Isoetharine, the bronchodilator in Bronkosol and Bronkometer, has minimal Beta1 activity, thus making it possible to select a drug for predominance of a desired effect. Beat by beat—breath by breath Bronkosol and Bronkometer promote airway clearance with minimal direct cardiostimulating action.

The Beta$_2$ Inhalant Solution

BRONKOSOL®

isoetharine 1.0%, phenylephrine HCl 0.25%

BRONKOMETER®

isoetharine 0.61% W/W, phenylephrine HCl 0.125% W/W

The Beta$_2$ Aerosol

The Beta$_2$ Bronchodilators

sympathomimetic amines, since overdosage may result in tachycardia, palpitation, nausea, headache, or epinephrine-like side effects.

Adverse Effects: Although Bronkosol and Bronkometer are relatively free of toxic side effects, too frequent use may cause tachycardia, palpitation, nausea, headache, changes in blood pressure, anxiety, tension, restlessness, insomnia, tremor, weakness, dizziness and excitement as is the case with other sympathomimetic amines.

Dosage and Administration: Bronkosol—Oral inhalation. Can be administered by hand nebulizer, oxygen aerosolization, or intermittent positive pressure breathing (IPPB). Usually treatment need not be repeated more often than every four hours, although in severe cases more frequent administration may be necessary.

Recommended Dosage: Bronkometer—The average adult dose is one or two inhalations. Occasionally, more may be required. It is important, however, to wait one full minute after the initial one or two inhalations in order to be certain whether another is necessary. In most cases, inhalations need not be repeated more often than every four hours, although more frequent administration may be necessary in severe cases.

How Supplied: Bronkosol® for inhalation — bottles of 10 ml. (Code No. 1711); Bronkometer® 10 ml. vial with Oral Nebulizer (Code No. 1701); Bronkometer® 20 ml. vial with Oral Nebulizer for desk or bedside (Code No. 1702); Bronkometer® 10 ml. refill only (Code No. 1703); Bronkometer® tpr Actuator and 10 ml. refill (Code No. 1704).

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The Editorial Board will be glad to receive and consider for publication letters containing information of general interest to physicians or presenting constructive criticisms on issues of the day.

"Entered as second class matter at the post office in San Francisco and additional mailing offices under the Act of March 3, 1879." Acceptance for mailing at special rate of postage provided for in Section 1103, Act of October 3, 1917, authorized August 10, 1918.

Antihypertensive action at the vasomotor centers in the brain*
*(Based on animal studies)
Please see last page of advertisement for a brief summary of the prescribing information including relationship of pharmacologic actions and antihypertensive effect.

Now... antihypertensive action at the vasomotor centers in the brain

new Catapres®

Tablets of 0.1 and 0.2 mg

(clonidine hydrochloride)

Effective in hypertension, mild to severe

Mild and infrequent orthostatic hypotension

Normal hemodynamic responses to exercise are unaffected

Renal blood flow and glomerular filtration rate essentially unchanged

Mild to moderate potency

Central action:

Catapres appears to lower blood pressure through central alpha-adrenergic stimulation, as shown in animal studies. This results in diminution—but not blocking—of sympathetic outflow from cardio-accelerator and vasoconstrictor centers in the medulla.

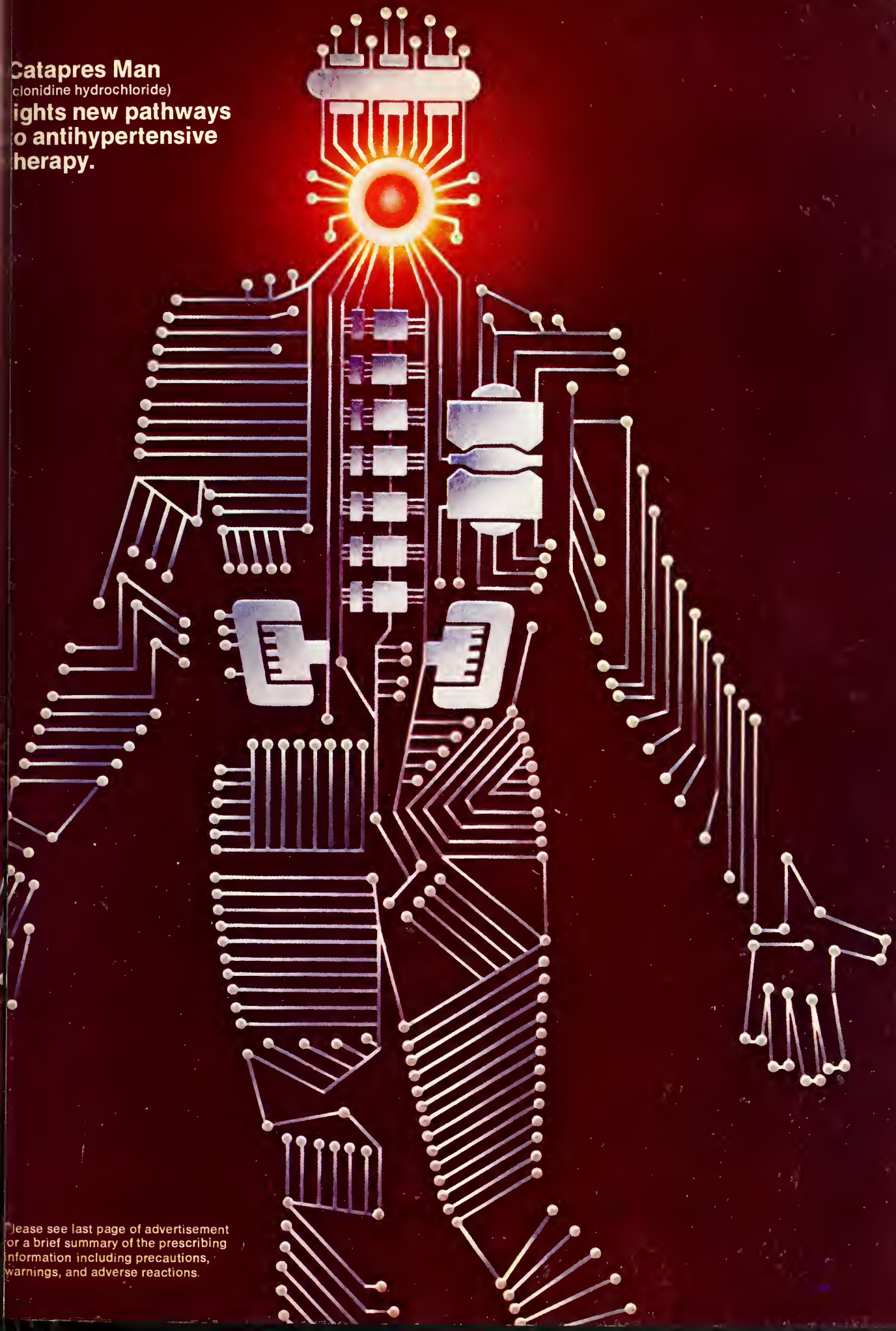
Not a "depleter"

Not a "blocker"

Not an "inhibitor"

Not a "false transmitter"

Catapres Man
(clonidine hydrochloride)
lights new pathways to antihypertensive therapy.



Please see last page of advertisement for a brief summary of the prescribing information including precautions, warnings, and adverse reactions.

new Catapres®
(clonidine hydrochloride)

Effective in hypertension, mild to severe

Catapres is distinguished by its broad clinical usefulness in the treatment of hypertension.

More than 600 major published papers*

The extensive experimental and clinical work with Catapres has been reported in hundreds of papers published in scientific journals in this country and abroad. Controlled studies[1-7] plus numerous other clinical evaluations have demonstrated that Catapres is an effective antihypertensive drug with these desirable properties:

does not alter normal hemodynamic responses to exercise

renal blood flow and glomerular filtration rate essentially unchanged

antihypertensive response enhanced by diuretics such as chlorthalidone

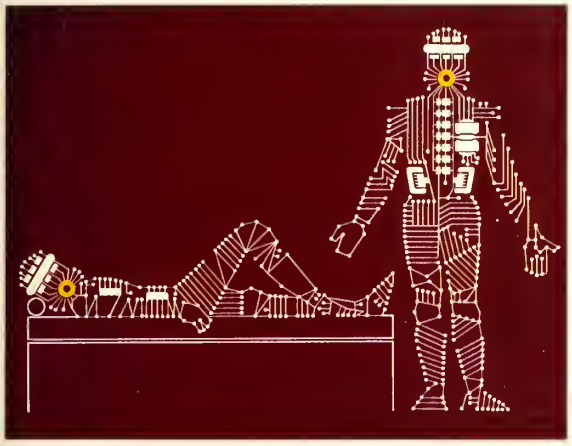
compatible with other antihypertensive agents

has been shown to reduce plasma renin activity and to decrease excretion of aldosterone and catecholamines
(See ACTIONS section of Brief Summary)

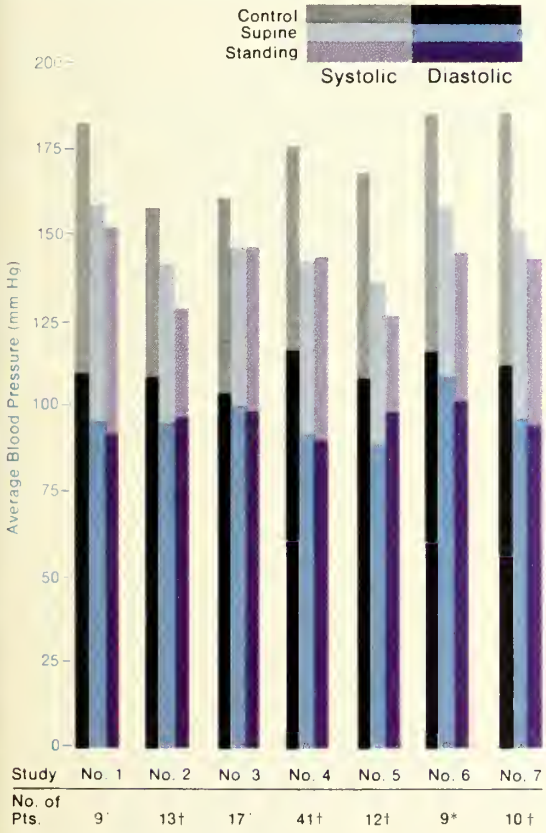
What to watch for—The principal side effects of Catapres are dry mouth, sedation, and drowsiness. Constipation, dizziness, headache, and fatigue also have been reported. Generally, these effects tend to diminish with continued therapy. As with other antihypertensive agents, tolerance may develop in some instances. For a more detailed discussion of side effects, warnings, and precautions, see the brief summary of prescribing information on the last page of this advertisement or consult the Catapres package insert.

*Complete Catapres bibliography available on request.

Mild and infrequent orthostatic effects

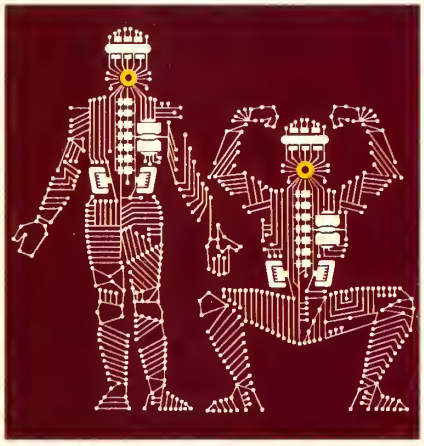


Standing and supine blood pressure response at the conclusion of therapy in 7 controlled studies[1-7]

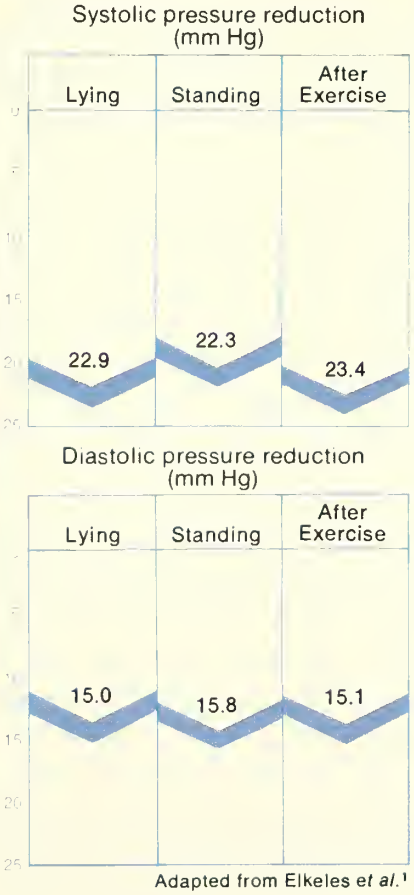


*Received Catapres alone.
†Received Catapres + a diuretic.
Note: In study No.4, blood pressure was taken in the sitting rather than the supine position.

Normal hemodynamic responses to exercise not altered

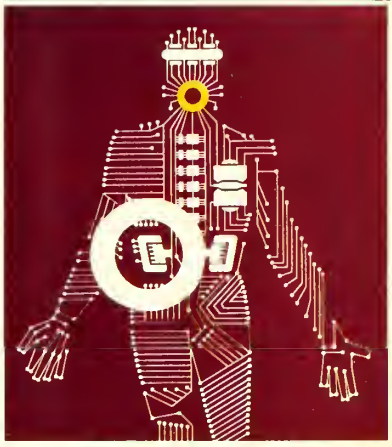


Mean blood pressure reductions in 9 hypertensive patients receiving Catapres (0.15 mg daily) for 4 weeks

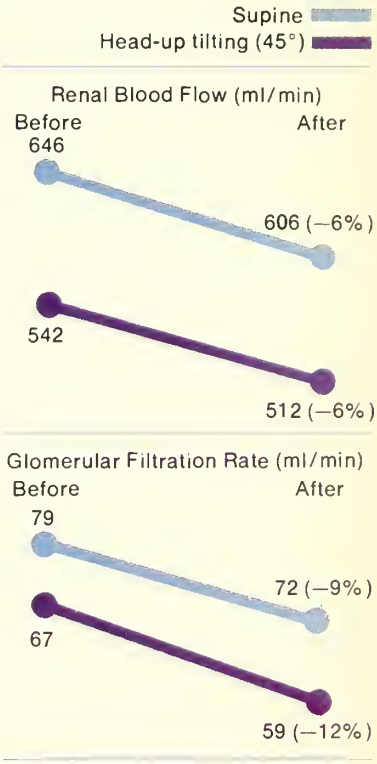


Adapted from Elkeles *et al.*[1]

Renal blood flow and glomerular filtration rate essentially unchanged

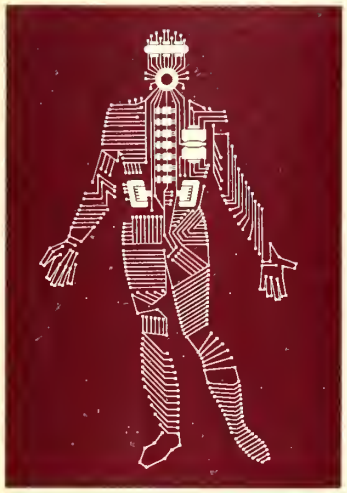


Renal hemodynamics before and after Catapres in 7 hypertensive patients. Mean blood pressure reductions were significant in both the supine position (from 155 to 128 mm Hg) and the standing position (from 151 to 101 mm Hg).



Adapted from Onesti *et al.*[8]

New from Boehringer Ingelheim



new Catapres®
(clonidine hydrochloride)

It's easy to start with Catapres. The usual starting dose of Catapres is one 0.1 mg tablet twice daily. Increments of 0.1 to 0.2 mg per day (up to the maximum daily dose of 2.4 mg) may be made until the desired blood pressure response is achieved.

How to stop Catapres. Reduce the dose gradually over two to four days to avoid a possible rapid rise in blood pressure and associated subjective symptoms such as nervousness, agitation, and headache. Patients on Catapres should be instructed not to discontinue therapy without consulting their physician. It has been demonstrated that a rapid rise in blood pressure, should it occur, can be reversed by resumption of Catapres or by administration of intravenous phentolamine.

Catapres®
(clonidine hydrochloride)
Tablets of 0.1 mg and 0.2 mg

Actions: The mechanism of action appears to be central alpha-adrenergic stimulation as demonstrated in animal studies. This results in inhibition of bulbar sympathetic cardioaccelerator and sympathetic vasoconstrictor centers, thereby decreasing sympathetic outflow from the brain. Other studies in humans have provided evidence of a reduction in plasma renin activity and the excretion of aldosterone and catecholamines. The exact relationship between these pharmacologic actions of Catapres (clonidine hydrochloride) in humans and its antihypertensive effect has not been fully elucidated at this time.

Indication: The drug is indicated in the treatment of hypertension. As an antihypertensive drug, Catapres (clonidine hydrochloride) is mild to moderate in potency. It may be employed in a general treatment program with a diuretic and/or other antihypertensive agents as needed for proper patient response.

Warnings: Tolerance may develop in some patients necessitating a reevaluation of therapy.
Usage in Pregnancy: In view of embryotoxic findings in animals, and since information on possible adverse effects in pregnant women is limited to uncontrolled clinical data, the drug is not recommended in women who are or may become pregnant unless the potential benefits outweigh the potential risk to mother and fetus.
Usage in Children: No clinical experience is available with the use of Catapres (clonidine hydrochloride) in children.

Precautions: When discontinuing Catapres (clonidine hydrochloride), reduce the dose gradually over 2 to 4 days to avoid a possible rapid rise in blood pressure and associated subjective symptoms such as nervousness, agitation, and headache. Patients should be instructed not to discontinue therapy without consulting their physician. Rare instances of hypertensive encephalopathy and death have been recorded after cessation of clonidine hydrochloride therapy. A causal relationship has not been established in these cases. It has been demonstrated that an excessive rise in blood pressure, should it occur, can be reversed by resumption of clonidine hydrochloride therapy or by intravenous phentolamine. Patients who engage in potentially hazardous activities, such as operating machinery or driving, should be advised of the sedative effect. This drug may enhance the CNS-depressive effects of alcohol, barbiturates and other sedatives. Like any other agent lowering blood pressure, clonidine hydrochloride should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease or chronic renal failure.

As an integral part of their overall long-term care, patients treated with Catapres (clonidine hydrochloride) should receive periodic eye examinations. While, except for some dryness of the eyes, no drug-related abnormal ophthalmologic findings have been recorded with Catapres (clonidine hydrochloride), in several studies the drug produced a dose-dependent increase in the incidence and severity of spontaneously occurring retinal degeneration in albino rats treated for 6 months or longer.

Adverse Reactions: The most common reactions are dry mouth, drowsiness and sedation. Constipation, dizziness, headache, and fatigue have been reported. Generally these effects tend to diminish with continued therapy. The following reactions have been associated with the drug, some of them rarely. (In some instances an exact causal relationship has not been established.) These include: Anorexia, malaise, nausea, vomiting, parotid pain, mild transient abnormalities in liver function tests; one report of possible drug-induced hepatitis without icterus and hyperbilirubinemia in a patient receiving clonidine hydrochloride, chlorthalidone, and papaverine hydrochloride. Weight gain, transient elevation of blood glucose, or serum creatine phosphokinase; congestive heart failure, Raynaud's phenomenon; vivid dreams or nightmares, insomnia, other behavioral changes, nervousness, restlessness, anxiety and mental depression. Also rash, angioneurotic edema, hives, urticaria, thinning of the hair, pruritus not associated with a rash, impotence, urinary retention, increased sensitivity to alcohol, dryness, itching or burning of the eyes, dryness of the nasal mucosa, pallor, gynecomastia, weakly positive Coombs' test, asymptomatic electrocardiographic abnormalities manifested as Wenckebach period or ventricular trigeminy.

Overdosage: Profound hypotension, weakness, somnolence, diminished or absent reflexes and vomiting followed the accidental ingestion of Catapres (clonidine hydrochloride) by several children from 19 months to 5 years of age. Gastric lavage and administration of an analeptic and vasopressor led to complete recovery within 24 hours. Tolazoline in intravenous doses of 10 mg at 30-minute intervals usually abolishes all effects of Catapres (clonidine hydrochloride) overdosage.

How Supplied: Catapres, brand of clonidine hydrochloride, is available as 0.1 mg (tan) and 0.2 mg (orange) oval, single-scored tablets in bottles of 100.

For complete details, please see full prescribing information.

Under license from Boehringer Ingelheim GmbH

References: 1. Elkeles, R. S., Goldby, F. S. and Oliver, D. O.: A Double Blind Study of Catapres, A New Hypotensive Agent, *in* Conolly, M. E. (ed.): Catapres in Hypertension, London, Butterworths, 1970, pp. 139-144. 2. Freis, E. D.: Data on file at Boehringer Ingelheim Ltd. 3. Hickler, R. B.: Data on file at Boehringer Ingelheim Ltd. 4. Mroczek, W. J., Leibel, B. A. and Finnerty, F. A., Jr.: Comparison of clonidine and methyldopa in hypertensive patients receiving a diuretic, Am. J. Cardiol. **29**:712, 1972. 5. Putzeys, M. R. and Hoobler, S. W.: Comparison of clonidine and methyldopa on blood pressure and side effects in hypertensive patients, Am. Heart J. **83**:464, 1972. 6. MacDonald, R. H. and Shapiro, A.: Data on file at Boehringer Ingelheim Ltd. 7. Kirkendall, W. M., Toubes, D. B. *et al.*: Hypertensive effects of clonidine and chlorthalidone, Am. Heart J. **82**:312, 1971. 8. Onesti, G. *et al.*: Pharmacodynamic effects of a new antihypertensive drug, Catapres (ST-155), Circulation **39**:219, 1969.

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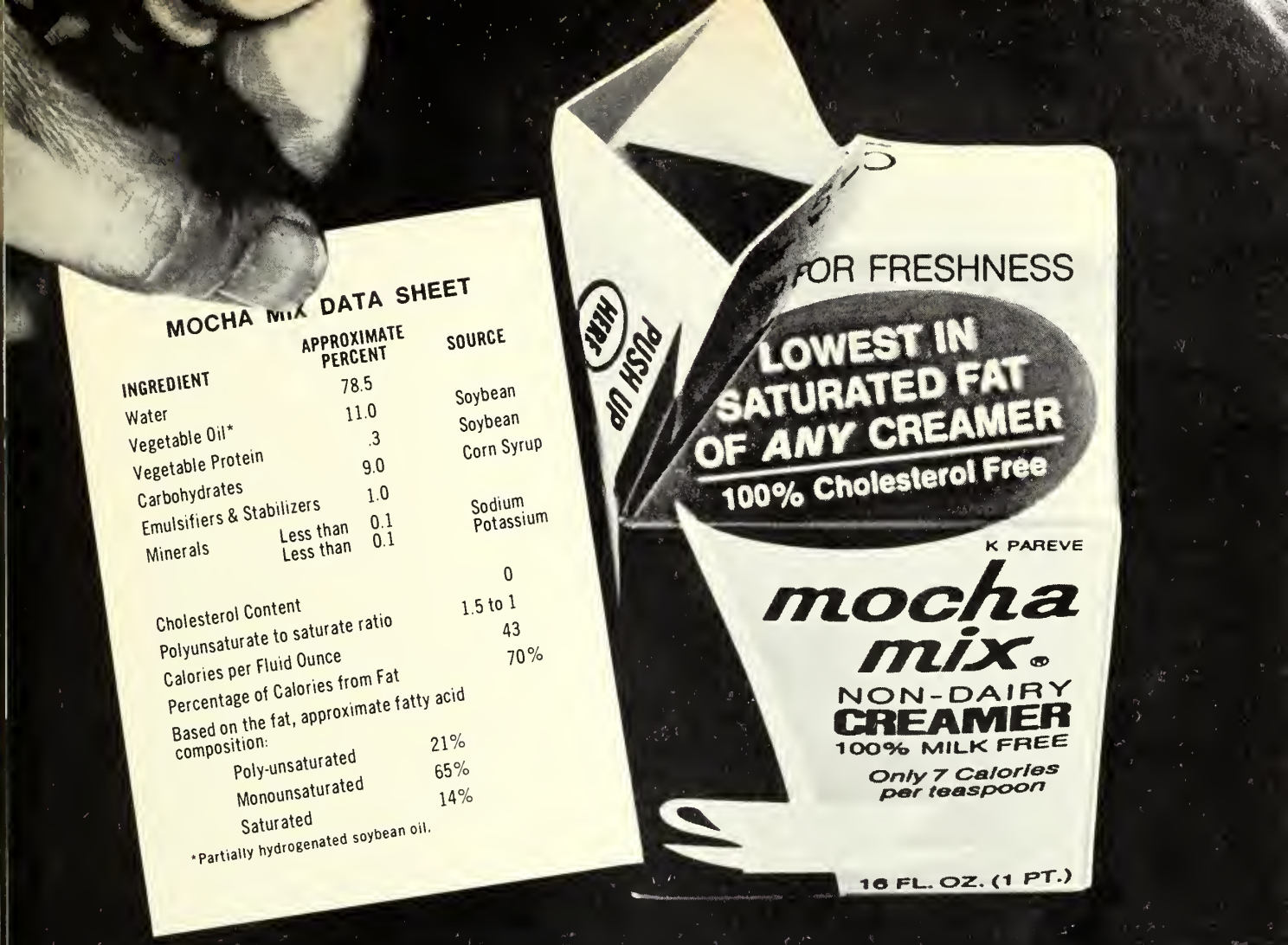

Mocha Mix® presents its credentials:

Study them. Note how low Mocha Mix® is in saturated fat. (Actually the lowest of any creamer — liquid, frozen or powdered.) Then note the unsaturated to saturated fat ratio (1.5:1). And Mocha Mix is 100% milk-free and 100% cholesterol-free, too! Taste? In coffee . . . on cereal, fruit or desserts . . . or for cooking, any way, any time a creamer is called for, Mocha Mix is the most delicious creamer ever!

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***mocha mix*. . . . the non-dairy creamer that's lowest in saturated fat!**

When diarrhea has his number...

Lomotil puts him back in the game.

Physicians and patients both want prompt control of the symptoms of diarrhea. A rapid, uncontrolled loss of fluids and electrolytes can cause a medical crisis, particularly in children, and in patients who are seriously ill, or in people who are badly undernourished.

Lomotil usually stops diarrhea promptly. This rapid action halts the emergency aspect of diarrhea and is comforting and reassuring to the patient. Electrolyte and fluid losses can be corrected while the specific cause of the diarrhea is being determined. If an infective agent is the cause, appropriate antibiotic therapy should be given along with Lomotil.

Lomotil has few side effects, and those that do occur are generally mild.

Lomotil®
TABLETS/LIQUID

Each tablet and each 5 ml. of liquid contain:
diphenoxylate hydrochloride ..... 2.5 mg.
(Warning: May be habit forming)
atropine sulfate ..... 0.025 mg.

Usually stops diarrhea promptly.

IMPORTANT INFORMATION: This is a Schedule V substance by Federal law; diphenoxylate HCl is chemically related to meperidine. In case of overdosage or individual hypersensitivity, reactions similar to those after meperidine or morphine overdosage may occur; treatment is similar to that for meperidine or morphine intoxication (prolonged and careful monitoring). Respiratory depression may recur in spite of an initial response to Nalline® (nalorphine HCl) or may be evidenced as late as 30 hours after ingestion. LOMOTIL IS NOT AN INNOCUOUS DRUG AND DOSAGE RECOMMENDATIONS SHOULD BE STRICTLY ADHERED TO, ESPECIALLY IN CHILDREN. THIS MEDICATION SHOULD BE KEPT OUT OF REACH OF CHILDREN.

Indications: Lomotil is effective as adjunctive therapy in the management of diarrhea.

Contraindications: In children less than 2 years, due to the decreased safety margin in younger age groups, and in patients who are jaundiced or hypersensitive to diphenoxylate HCl or atropine.

Warnings: Use with caution in young children, because of variable response, and with extreme caution in patients with cirrhosis and other advanced hepatic disease or abnormal liver function tests, because of possible hepatic coma. Diphenoxylate HCl may potentiate the action of barbiturates, tranquilizers and alcohol. In theory, the concurrent use with monoamine oxidase inhibitors could precipitate hypertensive crisis.

Usage in pregnancy: Weigh the potential benefits against possible risks before using during pregnancy, lactation or in women of childbearing age. Diphenoxylate HCl and atropine are secreted in the breast milk of nursing mothers.

Precautions: Addiction (dependency) to diphenoxylate HCl is theoretically possible at high dosage. Do not exceed recommended dosages. Administer with caution to patients receiving addicting drugs or known to be addiction prone or having a history of drug abuse. The subtherapeutic amount of atropine is added to discourage deliberate overdosage; strictly observe contraindications, warnings and precautions for atropine; use with caution in children since signs of atropinism may occur even with the recommended dosage.

Adverse reactions: Atropine effects include dryness of skin and mucous membranes, flushing and urinary retention. Other side effects with Lomotil include nausea, sedation, vomiting, swelling of the gums, abdominal discomfort, respiratory depression, numbness of the extremities, headache, dizziness, depression, malaise, drowsiness, coma, lethargy, anorexia, restlessness, euphoria, pruritus, angioneurotic edema, giant urticaria and paralytic ileus.

Dosage and administration: ***Lomotil is contraindicated in children less than 2 years old.*** Use only Lomotil liquid for children 2 to 12 years old. For ages 2 to 5 years, 4 ml. (2 mg.) t.i.d.; 5 to 8 years, 4 ml. (2 mg.) q.i.d.; 8 to 12 years, 4 ml. (2 mg.) 5 times daily; adults, two tablets (5 mg.) t.i.d. to two tablets (5 mg.) q.i.d. or two regular teaspoonfuls (10 ml., 5 mg.) q.i.d. Maintenance dosage may be as low as one fourth of the initial dosage. Make downward dosage adjustment as soon as initial symptoms are controlled.

Overdosage: Keep the medication out of the reach of children since accidental overdosage may cause severe, even fatal, respiratory depression. Signs of overdosage include flushing, lethargy or coma, hypotonic reflexes, nystagmus, pinpoint pupils, tachycardia and respiratory depression which may occur 12 to 30 hours after overdose. Evacuate stomach by lavage, establish a patent airway and, when necessary, assist respiration mechanically. Use a narcotic antagonist in severe respiratory depression. Observation should extend over at least 48 hours.

Dosage forms: Tablets, 2.5 mg. of diphenoxylate HCl with 0.025 mg. of atropine sulfate. *Liquid,* 2.5 mg. of diphenoxylate HCl and 0.025 mg. of atropine sulfate per 5 ml. A plastic dropper calibrated in increments of ½ ml. (total capacity, 2 ml.) accompanies each 2-oz. bottle of Lomotil liquid.

SEARLE **Searle & Co.**
San Juan, Puerto Rico 00936

Address medical inquiries to:
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Medical Department, Box 5110,
Chicago, Illinois 60680

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BOOKS RECEIVED

Books received by THE WESTERN JOURNAL OF MEDICINE *are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.*

ELECTROCARDIOGRAPHY—Practical Applications with Vectorial Principles—Edward K. Chung, MD, Professor of Medicine, Director of the Heart Station, Division of Cardiology, Department of Medicine, Thomas Jefferson University, The Jefferson Medical College, Philadelphia. Harper & Row, Publishers, Inc., Medical Department, 2350 Virginia Avenue, Hagerstown, MD (21740), 1974. 613 pages, with 200 illustrations, $30.00.

THE EFFECTS OF HOSPITALIZATION ON CHILDREN—Models for Their Care—Edited by Evelyn K. Oremland, MSW, and Jerome D. Oremland, MD, Faculty, San Francisco Psychoanalytic Institute, Chairman, Extension Division, Psychoanalytic Institute. Charles C Thomas, Publisher, 301-327 East Lawrence Avenue, Springfield, Ill (62703), 1973. 360 pages, $12.75.

THE ETIOLOGY OF HUMAN BREAST CANCER—Endocrine, Genetic, Viral, Immunologic and Other Considerations. Anaxagoras N. Papaioannou, MD, Chief of Surgery (B'Unit), "Evangelismos" Medical Center, Athens. Springer-Verlag, New York, Inc., 175 Fifth Avenue, New York City (10010), 1974. 216 pages, $23.00.

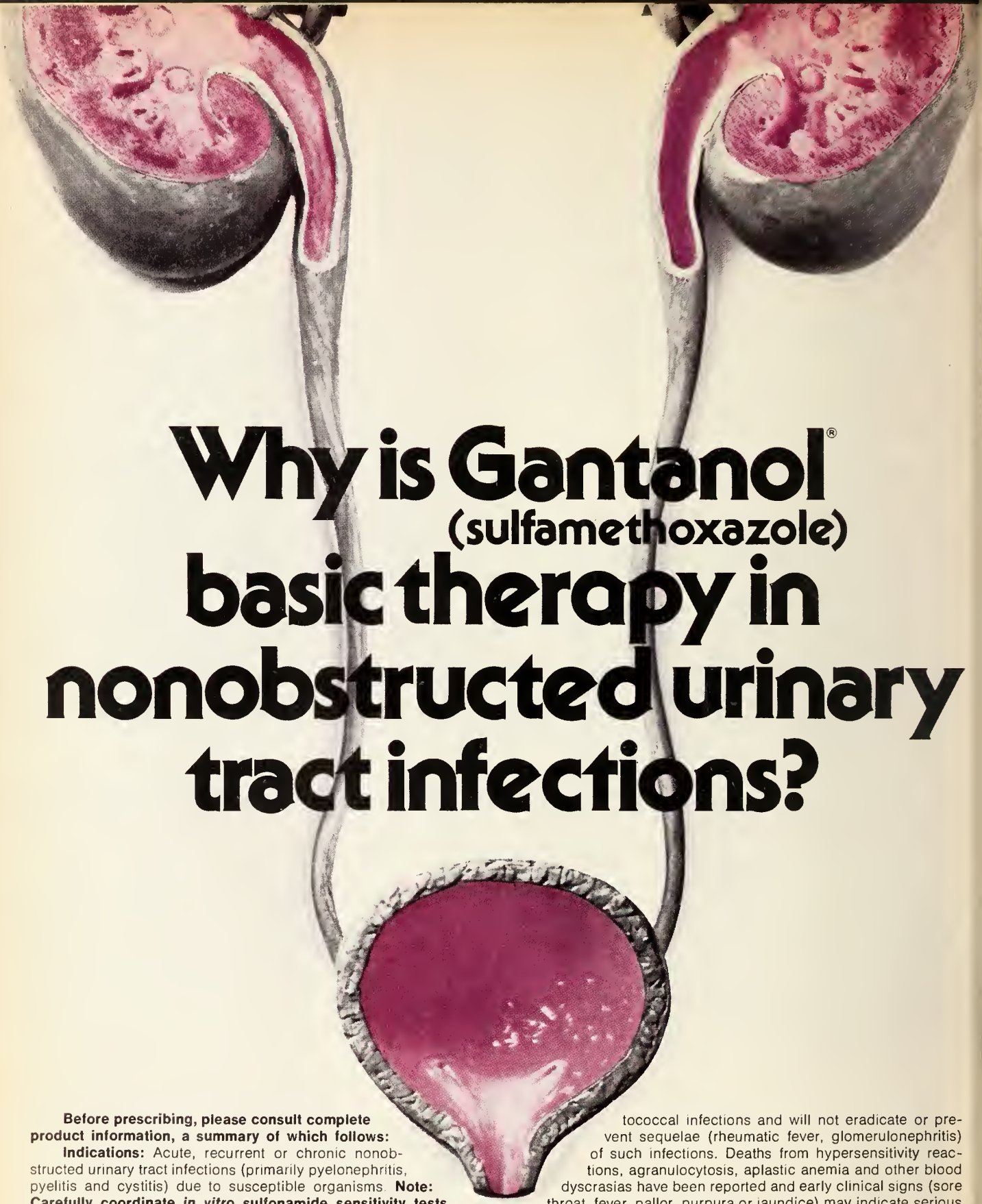
HANDBOOK OF PSYCHIATRY—Third Edition—Edited by Philip Solomon, MD, Clinical Professor of Psychiatry, University of California, San Diego, School of Medicine; and Vernon D. Patch, MD, Associate Professor of Psychiatry, Harvard Medical School, and Director, City of Boston Drug Treatment Center. Lange Medical Publications, Drawer L, Los Altos, CA (94022), 1974. 706 pages, $8.00.

IMMUNOLOGICAL ASPECTS OF SKIN DISEASES—Edited by Lionel Fry, BSc, MD, MRCP, and P. P. Seah, MB, MRCP, Department of Dermatology, St. Mary's Hospital, London. John Wiley & Sons, Inc., Publishers, 605 Third Avenue, New York City (10016), 1974. 289 pages, $19.95.

I THINK I CAN—William Breisky. Doubleday & Company, Inc., 245 Park Avenue, New York City (10017), 1974. 234 pages, $6.95.

MICROORGANISMS AND HUMAN DISEASE—Ernest Alan Meyer, ScD, Professor of Microbiology, Department of Microbiology, University of Oregon Medical School, Lecturer in Microbiology, University of Oregon School of Nursing. Appleton-Century-Crofts, A Publishing Division of Prentice-Hall, Inc., 292 Madison Avenue, New York City (10017), 1974. 451 pages, $15.00.

(Continued on Page 36)



Why is Gantanol® (sulfamethoxazole) basic therapy in nonobstructed urinary tract infections?

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Acute, recurrent or chronic nonobstructed urinary tract infections (primarily pyelonephritis, pyelitis and cystitis) due to susceptible organisms. **Note: Carefully coordinate *in vitro* sulfonamide sensitivity tests with bacteriologic and clinical response; add aminobenzoic acid to follow-up culture media. The increasing frequency of resistant organisms limits the usefulness of antibacterials including sulfonamides, especially in chronic or recurrent urinary tract infections.** Measure sulfonamide blood levels as variations may occur; 20 mg/100 ml should be maximum total level.

Contraindications: Sulfonamide hypersensitivity; pregnancy at term and during nursing period; infants less than two months of age.

Warnings: Safety during pregnancy has not been established. Sulfonamides should not be used for group A beta-hemolytic streptococcal infections and will not eradicate or prevent sequelae (rheumatic fever, glomerulonephritis) of such infections. Deaths from hypersensitivity reactions, agranulocytosis, aplastic anemia and other blood dyscrasias have been reported and early clinical signs (sore throat, fever, pallor, purpura or jaundice) may indicate serious blood disorders. Frequent CBC and urinalysis with microscopic examination are recommended during sulfonamide therapy. Insufficient data on children under six with chronic renal disease.

Precautions: Use cautiously in patients with impaired renal or hepatic function, severe allergy, bronchial asthma; in glucose-6-phosphate dehydrogenase-deficient individuals in whom dose-related hemolysis may occur. Maintain adequate fluid intake to prevent crystalluria and stone formation.

Adverse Reactions: *Blood dyscrasias* (agranulocytosis, aplastic anemia, thrombocytopenia, leukopenia, hemolytic anemia, pur-

Because it is considered a good choice...

- for efficacy in nonobstructed cystitis, pyelonephritis and pyelitis
- for control of susceptible *E. coli, Klebsiella-Aerobacter, Staph. aureus, Proteus mirabilis* and, less frequently, *Proteus vulgaris*
- for prompt antibacterial blood and urine levels in from 2 to 3 hours after initial 2-gram adult dose
- for economical around-the-clock coverage
- for maximum patient cooperation with easy-to-remember B.I.D. dosage

Basic Therapy

Gantanol®

(sulfamethoxazole)

Tablets/Suspension
(0.5 Gm) (0.5 Gm/teasp.)

pura, hypoprothrombinemia and methemoglobinemia); *allergic reactions* (erythema multiforme, skin eruptions, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis); *gastrointestinal reactions* (nausea, emesis, abdominal pains, hepatitis, diarrhea, anorexia, pancreatitis and stomatitis); *CNS reactions* (headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo and insomnia); *miscellaneous reactions* (drug fever, chills, toxic nephrosis with oliguria and anuria, periarteritis nodosa and L.E. phenomenon). Due to certain chemical similarities with some goitrogens, diuretics (acetazolamide, thiazides) and oral hypoglycemic agents, sulfonamides have caused rare instances of goiter production, diuresis and hypoglycemia as well as thyroid malignancies in rats following long-term administration. Cross-sensitivity with these agents may exist.

Dosage: Systemic sulfonamides are contraindicated in infants under 2 months of age (except adjunctively with pyrimethamine in congenital toxoplasmosis).

Usual adult dosage: 2 Gm (4 tabs or teasp.) initially, then 1 Gm *b.i.d.* or *t.i.d.* depending on severity of infection.

Usual child's dosage: 0.5 Gm (1 tab or teasp.)/20 lbs of body weight initially, then 0.25 Gm/20 lbs *b.i.d.* Maximum dose should not exceed 75 mg/kg/24 hrs.

Supplied: Tablets, 0.5 Gm sulfamethoxazole; Suspension, 0.5 Gm sulfamethoxazole/teaspoonful.

ROCHE

Roche Laboratories
Division of Hoffmann-La Roche Inc.
Nutley, N.J. 07110

Before prescribing, see complete prescribing information in SK&F literature or *PDR*. The following is a brief summary.

Indications: Edema associated with congestive heart failure, cirrhosis of the liver, the nephrotic syndrome; steroid-induced and idiopathic edema; edema resistant to other diuretic therapy. Also, mild to moderate hypertension.

Contraindications: Pre-existing elevated serum potassium. Hypersensitivity to either component. Continued use in progressive renal or hepatic dysfunction or developing hyperkalemia.

Warnings: Do not use dietary potassium supplements or potassium salts unless hypokalemia develops or dietary potassium intake is markedly impaired. Enteric-coated potassium salts may cause small bowel stenosis with or without ulceration. Hyperkalemia (>5.4 mEq/L) has been reported in 4% of patients under 60 years, in 12% of patients over 60 years, and in less than 8% of patients overall. Rarely, cases have been associated with cardiac irregularities. Accordingly, **check serum potassium during therapy, particularly in patients with suspected or confirmed renal insufficiency (e.g., elderly or diabetics). If hyperkalemia develops, substitute a thiazide alone. If spironolactone is used concomitantly with 'Dyazide', check serum potassium frequently**—both can cause potassium retention and sometimes hyperkalemia. Two deaths have been reported in patients on such combined therapy (in one, recommended dosage was exceeded; in the other, serum electrolytes were not properly monitored). Observe patients on 'Dyazide' regularly for possible blood dyscrasias, liver damage or other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving Dyrenium (triamterene, SK&F). Rarely, leukopenia, thrombocytopenia, agranulocytosis, and aplastic anemia have been reported with the thiazides. Watch for signs of impending coma in acutely ill cirrhotics. Thiazides are reported to cross the placental barrier and appear in breast milk. This may result in fetal or neonatal hyperbilirubinemia, thrombocytopenia, altered carbohydrate metabolism and possibly other adverse reactions that have occurred in the adult. When used during pregnancy or in women who might bear children, weigh potential benefits against possible hazards to fetus.

Precautions: Do periodic serum electrolyte and BUN determinations. Do periodic hematologic studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in postsympathectomy patients. The following may occur: hyperuricemia and gout, reversible nitrogen retention, decreasing alkali reserve with possible metabolic acidosis, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), digitalis intoxication (in hypokalemia). Use cautiously in surgical patients. Concomitant use with antihypertensive agents may result in an additive hypotensive effect.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis; rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting (may indicate electrolyte imbalance), diarrhea, constipation, other gastrointestinal disturbances. Rarely, necrotizing vasculitis, paresthesias, icterus, pancreatitis, and xanthopsia have occurred with thiazides alone.

Supplied: Bottles of 100 capsules; in Single Unit Packages of 100 (intended for institutional use only).

SK&F CO.
Carolina, P.R. 00630
Subsidiary of
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KEEP THE HYPERTENSIVE PATIENT ON THERAPY KEEP THERAPY SIMPLE WITH

DYAZIDE®

Trademark

Each capsule contains 50 mg. of Dyrenium* (brand of triamterene) and 25 mg. of hydrochlorothiazide.

Just 'Dyazide' once daily or twice daily
No inconvenient potassium supplements
Nor special K^+ rich diets needed as a rule

Two prime reasons patients drop out of hypertensive therapy are (1) the patient failed to understand directions, and (2) the regimen was overly complicated. Dosage is simple with 'Dyazide', easily understood, once or twice daily, depending on response. There's no need to complicate the regimen with potassium supplements or unwieldy potassium-rich diets.

TO KEEP BLOOD PRESSURE DOWN AND KEEP POTASSIUM LEVELS UP

Putting out the fires of arthritic pain
Rheumatoid arthritis can sometimes spread like wildfire, with joint after joint going up inflamed: "The usual onset is manifested by spotty joint involvement but an acute onset of symmetrical polyarthritis may be noted."*
If aspirin fails, consider Butazolidin alka. Giving one capsule four times a day often provides prompt, pain-relieving, anti-inflammatory action to help restore joint mobility. The results you can get within a week can be maintained on as little as one or two capsules daily.
Serious side effects can occur. Select patients carefully (particularly the elderly) and follow them closely in line with the drug's precautions, warnings, contraindications and adverse reactions. For full details, please read the prescribing information. It's summarized on the back of this page.
Butazolidin® alka
Each capsule contains:
100 mg. phenylbutazone USP
100 mg. dried aluminum hydroxide gel USP
150 mg. magnesium trisilicate USP
If it doesn't work in a week, forget it.

Important Note This drug is not a simple analgesic. Do not administer casually. Carefully evaluate patients before starting treatment and keep them under close supervision. Obtain a detailed history and complete physical and laboratory examination (complete hemogram, urinalysis, etc.) before prescribing and at frequent intervals thereafter. Carefully select patients, avoiding those responsive to routine measures, contraindicated patients or those who cannot be observed frequently. Warn patients not to exceed recommended dosage. Short-term relief of severe symptoms with the smallest possible dosage is the goal of therapy. Dosage should be taken with meals or a full glass of milk. Substitute alka capsules for tablets if dyspeptic symptoms occur. Patients should discontinue the drug and report immediately any sign of fever, sore throat, oral lesions (symptoms of blood dyscrasia), dyspepsia, epigastric pain, symptoms of anemia, black or tarry stools or other evidence of intestinal ulceration or hemorrhage, skin reactions, significant weight gain or edema. A one-week trial period is adequate. Discontinue in the absence of a favorable response. Restrict treatment periods to one week in patients over sixty.

Indications Rheumatoid arthritis, osteoarthritis, bursitis, acute gouty arthritis and rheumatoid spondylitis.

Contraindications Children 14 years or less, senile patients, history or symptoms of G.I. inflammation or ulceration including severe, recurrent or persistent dyspepsia, history or presence of drug allergy, blood dyscrasias, renal, hepatic or cardiac dysfunction, hypertension, thyroid disease, systemic edema, stomatitis and salivary gland enlargement due to the drug, polymyalgia rheumatica and temporal arteritis, patients receiving other potent chemotherapeutic agents, or long-term anticoagulant therapy.

Warnings Age, weight, dosage, duration of therapy, existance of concomitant diseases and concurrent potent chemotherapy affect incidence of toxic reactions. Carefully instruct and observe the individual patient, especially the aging (forty years and over) who have increased susceptibility to the toxicity of the drug. Use lowest effective dosage. Weigh initially unpredictable benefits against potential risk of severe, even fatal, reactions. The disease condition itself is unaltered by the drug. Use with caution in first trimester of pregnancy and in nursing mothers. Drug may appear in cord blood and breast milk. Serious, even fatal, blood dyscrasias, including aplastic anemia, may occur suddenly despite regular hemograms, and may become manifest days or weeks after cessation of drug. Any significant change in total white count, relative decrease in granulocytes, appearance of immature forms, or fall in hematocrit should signal immediate cessation of therapy and complete hematologic investigation. Unexplained bleeding involving CNS, adrenals and G.I. tract has occurred. The drug may potentiate action of insulin, sulfonylurea, and sulfonamide-type agents. Carefully observe patients taking these agents. Nontoxic and toxic goiters and myxedema have been reported (the drug reduces iodine uptake by the thyroid). Blurred vision can be a significant toxic symptom worthy of a complete ophthalmological examination. Swelling of ankles or face in patients under sixty may be prevented by reducing dosage. If edema occurs in patients over sixty, discontinue drug.

Precautions The following should be accomplished at regular intervals. Careful detailed history for disease being treated and detection of earliest signs of adverse reactions, complete physical examination including check of patient's weight, complete weekly (especially for the aging) or an every two week blood check, pertinent laboratory studies. Caution patients about participating in activity requiring alertness and coordination, as driving a car, etc. Cases of leukemia have been reported in patients with a history of short- and long-term therapy. The majority of these patients were over forty. Remember that arthritic-type pains can be the presenting symptom of leukemia.

Adverse Reactions This is a potent drug, its misuse can lead to serious results. Review detailed information before beginning therapy. Ulcerative esophagitis, acute and reactivated gastric and duodenal ulcer with perforation and hemorrhage, ulceration and perforation of large bowel, occult G.I. bleeding with anemia, gastritis, epigastric pain, hematemesis, dyspepsia, nausea, vomiting and diarrhea, abdominal distention, agranulocytosis, aplastic anemia, hemolytic anemia, anemia due to blood loss including occult G.I. bleeding, thrombocytopenia, pancytopenia, leukemia, leukopenia, bone marrow depression, sodium and chloride retention, water retention and edema, plasma dilution, respiratory alkalosis, metabolic acidosis, fatal and nonfatal hepatitis (cholestasis may or may not be prominent), petechiae, purpura without thrombocytopenia, toxic pruritus, erythema nodosum, erythema multiforme, Stevens-Johnson syndrome, Lyell's syndrome (toxic necrotizing epidermolysis), exfoliative dermatitis, serum sickness, hypersensitivity angiitis (polyarteritis), anaphylactic shock, urticaria, arthralgia, fever, rashes (all allergic reactions require prompt and permanent withdrawal of the drug), proteinuria, hematuria, oliguria, anuria, renal failure with azotemia, glomerulonephritis, acute tubular necrosis, nephrotic syndrome, bilateral renal cortical necrosis, renal stones, ureteral obstruction with uric acid crystals due to uricosuric action of drug, impaired renal function, cardiac decompensation, hypertension, pericarditis, diffuse interstitial myocarditis with muscle necrosis, perivascular granulomata, aggravation of temporal arteritis in patients with polymyalgia rheumatica, optic neuritis, blurred vision, retinal hemorrhage, toxic amblyopia, retinal detachment, hearing loss, hyperglycemia, thyroid hyperplasia, toxic goiter, association of hyperthyroidism and hypothyroidism (causal relationship not established), agitation, contusional states, lethargy, CNS reactions associated with overdosage, including convulsions, euphoria, psychosis, depression, headaches, hallucinations, giddiness, vertigo, coma, hyperventilation, insomnia, ulcerative stomatitis, salivary gland enlargement.

(B)98-146-070-J (10/71)

For complete details, including dosage, please see full prescribing information.

GEIGY Pharmaceuticals
Division of CIBA-GEIGY Corporation
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STANFORD UNIVERSITY SCHOOL OF MEDICINE

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This five-day interdepartmental course is a concise but comprehensive review of basic medical science and is designed to meet the needs of those clinicians who wish to expand their knowledge of molecular biology. Early registration is advised as attendance is limited. Tuition fee is $250 payable upon application for enrollment.

COURSE CONTENT

General lectures will cover: a review of chemistry and physics for clinicians, chemical bonds of biological importance, subatomic particles, correlation of cell structure and function, the structure and function of proteins, sugars and lipids, the structure of nucleic acids, DNA synthesis, expression of genetic information, regulation of gene expression, evolution of proteins, carbohydrate and fat metabolism, bioenergetics, neuroendocrine relationships, neurobiology—structure and development, neurobiology—function, neurobiology—a cellular approach to the nervous system, mutagenic hazards.

Elective sessions will include: the biology of water, structure of matter, bacterial antibiotic resistance, salt and water, interferon, blood coagulation, gastrointestinal immunity, energy supply and the design of the brain, tumor virus, genetics and disease, rheumatic disorders, organ morphogenesis, nutrition, enzymes and their actions, prostaglandins, atherosclerosis, hypertension, renin, and aldosterone, chromosomes and disease, mechanisms of immunity, genetics—problems and opportunities, nerve growth, hormones and their actions, molecular mechanisms of drug actions, biological membranes.

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MANAGEMENT OF THE SURGICAL PATIENT

AT MAUNA KEA BEACH HOTEL • APRIL 26 - MAY 3, 1975

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- **Once-a-day dosage schedule for adult outpatients**
  Therapy should be initiated with 50 mg to 100 mg at bedtime. This may be increased by 25 or 50 mg added to the bedtime dose as necessary to a maximum daily dose of 150 mg. The usual maintenance dose is 50 to 100 mg a day given at bedtime, though in some patients, 40 mg per day is sufficient.

- **Greater patient compliance**
  The simplicity of once-a-day dosage at bedtime makes it easier for patients to adhere to a regimen—an especially important consideration in depressed patients whose self-motivation may be at a low ebb.

Should not be used during the acute recovery phase following myocardial infarction; in patients hypersensitive to it; in those who have received an MAOI within two weeks; or in children under 12. Patients with cardiovascular disorders should be watched closely. Safe use during pregnancy and lactation has not been established. The drug may impair mental or physical abilities required in the performance of hazardous tasks and may enhance the response to alcohol. Since suicide is a possibility in any depressive illness, patients should not have access to large quantities of the drug. Hospitalize as soon as possible any patient suspected of having taken an overdose.

once a day at bedtime

Please see addendum on following page for other details of dosage and administration including divided daily doses, dosage in hospitalized patients, and dosage in elderly and adolescent patients.

TABLETS: 10 mg, 25 mg, and 50 mg INJECTION: 10 mg per ml

ELAVIL®

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MERCK SHARP & DOHME

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added dosage versatility in clinically significant depression

Contraindications: Known hypersensitivity. Should not be given concomitantly with a monoamine oxidase inhibitor or within at least 14 days following the discontinuance of a monoamine oxidase inhibitor since hyperpyretic crises, severe convulsions, and deaths have occurred. When used to replace a monoamine oxidase inhibitor, initiate dosage of amitriptyline HCl cautiously with gradual increase in dosage until optimum response is achieved. Not recommended during the acute recovery phase following myocardial infarction.

Warnings: May block the antihypertensive action of guanethidine or similarly acting compounds. Should be used with caution in patients with a history of seizures or urinary retention, or with angle-closure glaucoma or increased intraocular pressure; in patients with angle-closure glaucoma, even average doses may precipitate an attack. Patients with cardiovascular disorders should be watched closely; arrhythmias, sinus tachycardia, and prolongation of the conduction time have been reported, particularly with high doses; myocardial infarction and stroke have been reported with drugs of this class. Close supervision is required for hyperthyroid patients or those receiving thyroid medication. May impair mental and/or physical abilities required for performance of hazardous tasks, such as operating machinery or driving a motor vehicle. Safe use during pregnancy and lactation has not been established; in pregnant patients, nursing mothers, or women who may become pregnant, weigh possible benefits against possible hazards to mother and child. Not recommended for patients under 12 years of age.

Precautions: Schizophrenic patients may develop increased symptoms of psychosis; patients with paranoid symptomatology may have an exaggeration of such symptoms; manic depressive patients may experience a shift to the manic phase. In these circumstances, the dose of amitriptyline HCl may be reduced or a major tranquilizer, such as perphenazine, may be administered concurrently.

When given with anticholinergic agents or sympathomimetic drugs, including epinephrine combined with local anesthetics, close supervision and careful adjustment of dosages are required. Use cautiously in patients receiving large doses of ethchlorvynol, since transient delirium has been reported on concurrent administration. May enhance the response to alcohol and the effects of barbiturates and other CNS depressants. The possibility of suicide in depressed patients remains during treatment and until significant remission occurs; this type of patient should not have easy access to large quantities of the drug. Concurrent electroshock therapy may increase the hazards associated with such therapy; such treatment should be limited to patients for whom it is essential. When possible, discontinue the drug several days before elective surgery. Both elevation and lowering of blood sugar levels have been reported.

Adverse Reactions: *Note:* Included in this listing are a few adverse reactions not reported with this specific drug. However, pharmacological similarities among the tricyclic antidepressant drugs require that each reaction be considered when amitriptyline is administered. *Cardiovascular:* Hypotension, hypertension, tachycardia, palpitation, myocardial infarction, arrhythmias, heart block, stroke. *CNS and Neuromuscular:* Confusional states; disturbed concentration; disorientation; delusions; hallucinations; excitement; anxiety; restlessness; insomnia; nightmares; numbness, tingling, and paresthesias of the extremities; peripheral neuropathy; incoordination; ataxia; tremors; seizures; alteration in EEG patterns; extrapyramidal symptoms; tinnitus. *Anticholinergic:* Dry mouth, blurred vision, disturbance of accommodation, constipation, paralytic ileus, urinary retention, dilatation of urinary tract. *Allergic:* Skin rash, urticaria, photosensitization, edema of face and tongue. *Hematologic:* Bone marrow depression including agranulocytosis, leukopenia, eosinophilia, purpura, thrombocytopenia. *Gastrointestinal:* Nausea, epigastric distress, vomiting, anorexia, stomatitis, peculiar taste, diarrhea, parotid swelling, black tongue. *Endocrine:* Testicular swelling and gynecomastia in the male, breast enlargement and galactorrhea in the female, increased or decreased libido, elevation and lowering of blood sugar levels. *Other:* Dizziness, weakness, fatigue, headache, weight gain or loss, increased perspiration, urinary frequency, mydriasis, drowsiness, jaundice, alopecia. *Withdrawal Symptoms:* Abrupt cessation of treatment after prolonged administration may produce nausea, headache, and malaise; these are not indicative of addiction.

Overdosage: Hospitalize as soon as possible all patients suspected of having taken an overdose. Treatment is symptomatic and supportive. In addition, the intravenous administration of 1 to 3 mg physostigmine salicylate has been reported to reverse the symptoms of tricyclic antidepressant poisoning.

How Supplied: Tablets containing 10 mg and 25 mg amitriptyline HCl, in single-unit packages of 100 and bottles of 100, 1000, and 5000; tablets containing 50 mg amitriptyline HCl, in single-unit packages of 100 and bottles of 100 and 1000; for intramuscular use, in 10-ml vials containing per ml: 10 mg amitriptyline HCl, 44 mg dextrose, 1.5 mg methylparaben and 0.2 mg propylparaben as preservatives, and water for injection q.s. 1 ml.

For more detailed information, consult your MSD representative or see full prescribing information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, Pa. 19486

addendum

MSD MERCK SHARP & DOHME

ELAVIL®
(AMITRIPTYLINE HCl | MSD)

dosage forms for differing patient needs

25 mg (yellow)

This tablet may prove useful for initial therapy in adult outpatients. Starting dosage is usually 75 mg daily in divided doses or 50 to 100 mg once a day at bedtime. If necessary, this dosage may be increased gradually to a total of 150 mg a day. When doses are divided, dosage increases are made preferably in the late afternoon or at bedtime. A sedative effect may be apparent before the antidepressant effect is noted. An adequate therapeutic effect may take as long as 30 days to develop.

50 mg (beige)

The 50-mg tablet may be advantageous whenever higher dosages are required, or when the single daily dose is given at bedtime. The 50-mg tablet may also be convenient for many hospitalized patients who may need 100 mg a day initially. In these patients, dosage may be increased gradually to 200 mg a day if necessary. A small number of hospitalized patients may need as much as 300 mg a day.

10 mg (blue)

Because lower doses are generally recommended for adolescents and elderly patients, the 10-mg tablets may be most serviceable. Ten mg three times a day with 20 mg at bedtime may be satisfactory in adolescent and elderly patients who do not tolerate higher doses.

INJECTION
10 mg per ml

For patients unable or unwilling to take tablets, the injectable form may be suitable initially. The tablets should replace the injection as soon as possible. Initial intramuscular dosage is 20 to 30 mg (2 to 3 ml) four times a day. When Injection ELAVIL is administered intramuscularly, the effects may appear more rapidly than with oral administration.

Usage in Children: In view of the lack of experience in children, this drug is not recommended at the present time for patients under 12 years of age.

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Servings per container	32
Calories	100
Protein	0 grams
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Fat	11 grams
*Percent of calories from fat	99%
*Polyunsaturated	3 grams
*Saturated	2 grams
*Cholesterol	0 (0 per 100 grams)
Sodium	120 milligrams (865 mg./100 gm.)

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Vitamin A 10%

Contains less than 2 percent of the U.S. RDA of protein, Vitamin C, thiamine, riboflavin, niacin, Calcium, and iron

*Information on fat and cholesterol content is provided for individuals who, on the advice of a physician, are modifying their total dietary intake of fat and cholesterol

IMPERIAL

Nutrition Information Per Serving

Serving size	14 grams (about one tablespoon)
Servings per container	32 (per pound container)
Calories	100
Protein	0 (not a significant source of protein)
Carbohydrate	0
Fat	11 grams
Percent of calories from fat	over 99%
**Polyunsaturated	3 grams
**Saturated	2 grams
**Cholesterol	0 (0 per 100 grams)

*Percentage of U.S. recommended daily allowances (U.S. RDA)**

Vitamin A 10% Vitamin D 15%

*Contains less than 2 percent of the U.S. RDA of Vitamin C, thiamine, riboflavin, niacin, calcium, and iron.

**Information of fat and cholesterol content is provided for individuals who, on the advice of a physician, are modifying their total dietary intake of fat and cholesterol.

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Nutrition Information Per Serving

Serving size	14 grams (about one tablespoon)
Servings per container	32 (per pound container)
Calories	100
Protein	0
Carbohydrate	0
Fat	11 grams
Percent of calories from fats	100%
Polyunsaturated	5 grams
Saturated	2 grams
Contains no cholesterol	

Information of fat and cholesterol content is provided for individuals who, on the advice of a physician, are modifying their total dietary intake of fat and cholesterol

Percentage of U.S. recommended daily allowances (U.S. RDA)

Vitamin A 10% Vitamin E 15%

Contains less than 2 percent of the U.S. RDA of protein, Vitamin C, thiamine, riboflavin, niacin, calcium, and iron

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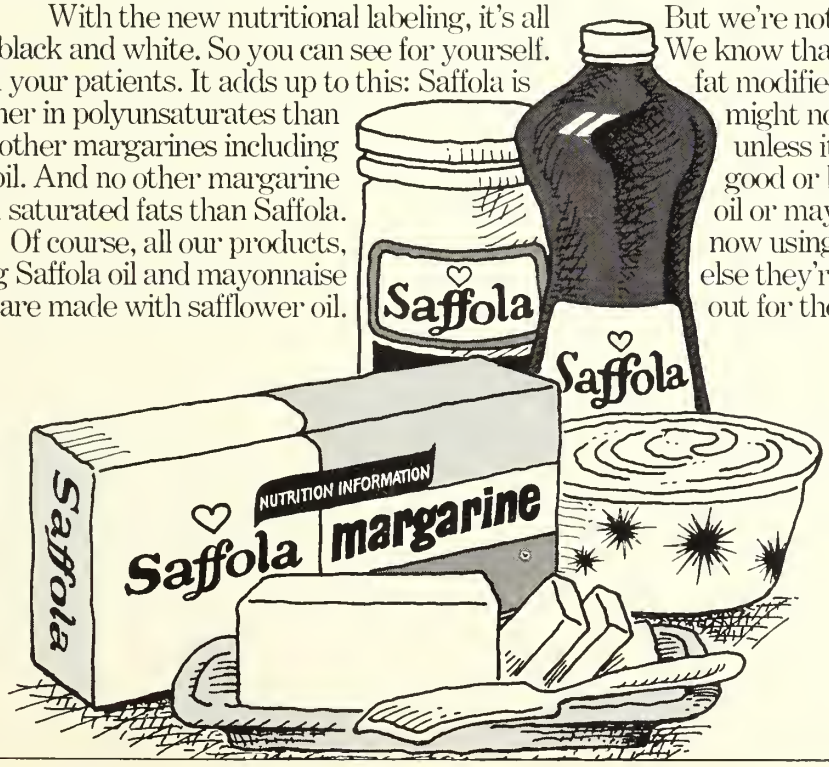

IN GONORRHEA

INJECTION

Wycillin®

(STERILE PROCAINE PENICILLIN G SUSPENSION) WYETH

Gonorrhea, according to the national Center for Disease Control, is, if the parenteral route is chosen, most effectively treated with aqueous procaine penicillin G. In uncomplicated cases, administration of 4.8 million units together with 1 gram oral probenecid, given at least 30 minutes prior to injection, is recommended.

Indications: In treatment of moderately severe infections due to penicillin G-sensitive microorganisms sensitive to the low and persistent serum levels common to this particular dosage form. Therapy should be guided by bacteriological studies (including sensitivity tests) and by clinical response.

NOTE: When high sustained serum levels are required use aqueous penicillin G, IM or IV.

The following infection will usually respond to adequate dosages of intramuscular procaine penicillin G.—*N. gonorrhoeae:* acute and chronic (without bacteremia).

FOR DEEP INTRAMUSCULAR INJECTION ONLY.

Contraindications: Previous hypersensitivity reaction to any penicillin.

Warnings: Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy.

Serious anaphylactoid reactions require immediate emergency treatment with epinephrine. Oxygen and intravenous corticosteroids should also be administered as indicated.

Although anaphylaxis is more frequent following parenteral therapy it has occurred in patients on oral penicillins. These reactions are more apt to occur in individuals with a history of sensitivity to multiple allergens.

There have been well documented reports of individuals with a history of penicillin hypersensitivity reactions who have experienced severe hypersensitivity reactions when treated with a cephalosporin. Before therapy with a penicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, and other allergens. If an allergic reaction occurs, the drug should be discontinued and the patient treated with the usual agents e.g., pressor amines, antihistamines and corticosteroids.

Precautions: Use cautiously in individuals with histories of significant allergies and/or asthma.

Carefully avoid intravenous or intraarterial use, or injection into or near major peripheral nerves or blood vessels, since such injections may produce neurovascular damage.

A small percentage of patients are sensitive to procaine. If there is a history of sensitivity, make the usual test: Inject intradermally 0.1 cc. of a 1 to 2 percent procaine solution. Development of an erythema, wheal, flare or eruption indicates procaine sensitivity. Sensitivity should be treated by the usual methods, including barbiturates, and procaine penicillin preparations should not be used. Antihistaminics appear beneficial in treatment of procaine reaction.

The use of antibiotics may result in overgrowth of nonsusceptible organisms. Constant observation of the patient is essential. If new infections due to bacteria or fungi appear during therapy, discontinue penicillin and take appropriate measures.

If allergic reaction occurs, withdraw penicillin unless, in the opinion of the physician, the condition being treated is life threatening and amenable only to penicillin therapy.

When treating gonococcal infections with suspected primary or secondary syphilis, perform proper diagnostic procedures, including darkfield examinations. In all cases in which concomitant syphilis is suspected, perform monthly serological tests for at least four months.

Adverse Reactions: (Penicillin has significant index of sensitization) skin rashes, ranging from maculopapular eruptions to exfoliative dermatitis; urticaria; serum sickness-like reactions, including chills, fever, edema, arthralgia and prostration. Severe and often fatal anaphylaxis has been reported. (See "Warnings.")

As with other antisyphilitics, Jarisch-Herxheimer reaction has been reported.

Administration and Dosage: Administer only by *deep intramuscular injection,* in upper outer quadrant of buttock. In infants and small children, midlateral aspect of thigh may be preferable. When doses are repeated, vary injection site. Before injection, aspirate to be sure needle bevel is not in blood vessel. If blood appears, remove needle and inject in another site.

Although some isolates of *Neisseria gonorrhoeae* have decreased susceptibility to penicillin, this resistance is relative, not absolute, and penicillin in large doses remains the drug of choice. Physicians are cautioned not to use less than recommended doses.

Gonorrheal infections (uncomplicated)—Men or Women: 4.8 million units intramuscularly divided into at least two doses and injected at different sites at one visit, together with 1 gram of oral probenecid, preferably given at least 30 minutes prior to injection.

NOTE: Treatment of severe complications of gonorrhea should be individualized using large amounts of short-acting penicillin. Gonorrheal endocarditis should be treated intensively with aqueous penicillin G. Prophylactic or epidemiologic treatment for gonorrhea (male and female) is accomplished with same treatment schedules as for uncomplicated gonorrhea.

Retreatment: The National Center for Disease Control, Venereal Disease Branch, U.S. Dept. H.E.W. recommends:

Test cure procedures at approximately 7-14 days after therapy. In the male, a gram-stained smear is adequate if positive; otherwise, a culture specimen should be obtained from the anterior urethra. In the female, culture specimens should be obtained from both the endocervical and anal canal sites.

Retreatment in males is indicated if urethral discharge persists 3 or more days following initial therapy and smear or culture remains positive. Follow-up treatment consists of 4.8 million units. I.M. divided in 2 injection sites at single visit.

In uncomplicated gonorrhea in the female, retreatment is indicated if follow-up cervical or rectal cultures remain positive for *N. gonorrhoeae.* Follow-up treatment consists of 4.8 million units daily on 2 successive days.

Syphilis: all gonorrhea patients should have a serologic test for syphilis at the time of diagnosis. Patients with gonorrhea who also have syphilis should be given additional treatment appropriate to the stage of syphilis.

Composition: Each TUBEX® disposable syringe 2,400,000 units (4-cc. size) contains procaine penicillin G in a stabilized aqueous suspension with sodium citrate buffer, and as w/v approximately 0.7% lecithin, 0.4% carboxymethylcellulose, 0.4% polyvinylpyrrolidone, 0.01% propylparaben and 0.09% methylparaben. The multiple-dose 10-cc. vial contains per cc. 300,000 units procaine penicillin G in a stabilized aqueous suspension with sodium citrate buffer and approximately 7 mg. lecithin, 2 mg. carboxymethylcellulose, 3 mg. polyvinylpyrrolidone, 0.5 mg. sorbitan monopalmitate, 0.5 mg. polyoxyethylene sorbitan monopalmitate, 0.14 mg. propylparaben and 1.2 mg. methylparaben.

Five are graduating with honors. How many with VD?

On the average, you can figure the incidence of VD among teenagers at about 900 per 100,000 population.* And growing.

Among those in the 20-24 age-group, the incidence is even higher. And it, too, is growing.

In the long run, a populace educated to the risks and prevention of VD is probably the best answer to the problem. Meanwhile, though, adequate doses of the recommended types of penicillin remain a formidable weapon.

IN SYPHILIS
INJECTION
Bicillin® LONG-ACTING
(STERILE BENZATHINE PENICILLIN G SUSPENSION) WYETH

Syphilis is preferably treated with benzathine penicillin G, which is also the drug of choice for prophylaxis after exposure. Administration of 2.4 million units (1.2 million in each buttock) usually cures most cases of primary, secondary and latent syphilis with negative spinal fluid.

Indications: In treatment of infections due to penicillin G-sensitive microorganisms that are susceptible to the low and very prolonged serum levels common to this particular dosage form. Therapy should be guided by bacteriological studies (including sensitivity tests) and by clinical response.

The following infections will usually respond to adequate dosage of intramuscular benzathine penicillin G.—Venereal infections: Syphilis, yaws, bejel and pinta.

FOR DEEP INTRAMUSCULAR INJECTION ONLY.

Contraindications: Previous hypersensitivity reaction to any penicillin.

Warnings: Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported. Anaphylaxis is more frequent following parenteral therapy but has occurred with oral penicillins. These reactions are more apt to occur in individuals with history of sensitivity to multiple allergens.

Severe hypersensitivity reactions with cephalosporins have been well documented in patients with history of penicillin hypersensitivity. Before penicillin therapy, carefully inquire into previous hypersensitivity to penicillins, cephalosporins and other allergens. If allergic reaction occurs, discontinue drug and treat with usual agents, e.g., pressor amines, antihistamines and corticosteroids.

Precautions: Use cautiously in individuals with histories of significant allergies and/or asthma.

Carefully avoid intravenous or intraarterial use, or injection into or near major peripheral nerves or blood vessels, since such injection may produce neurovascular damage.

In streptococcal infections, therapy must be sufficient to eliminate the organism; otherwise the sequelae of streptococcal disease may occur. Take cultures following completion of treatment to determine whether streptococci have been eradicated.

Prolonged use of antibiotics may promote overgrowth of nonsusceptible organisms including fungi. Take appropriate measures should superinfection occur.

Adverse Reactions: Hypersensitivity reactions reported are skin eruptions (maculopapular to exfoliative dermatitis), urticaria and other serum sickness reactions, laryngeal edema and anaphylaxis. Fever and eosinophilia may frequently be only reaction observed. Hemolytic anemia, leucopenia, thrombocytopenia, neuropathy and nephropathy are infrequent and usually associated with high doses of parenteral penicillin.

As with other antisyphilitics, Jarisch-Herxheimer reaction has been reported.

Administration and Dosage: Venereal infections—

Syphilis—Primary, secondary and latent—2.4 million units (1 dose).

Late (tertiary and neurosyphilis)—2.4 million units at 7 day intervals for three doses.

Congenital—under 2 years of age, 50,000 units/Kg. body weight; ages 2-12 years, adjust dosage based on adult dosage schedule.

(Shake multiple-dose vial vigorously before withdrawing the desired dose.) Administer by **deep intramuscular injection** in the upper outer quadrant of the buttock. In infants and small children, the midlateral aspect of the thigh may be preferable. When doses are repeated, vary the injection site. Before injecting the dose, aspirate to be sure needle bevel is not in a blood vessel. If blood appears, remove the needle and inject in another site.

Composition: 2,400,000 units in 4-cc. single dose disposable syringe. Each TUBEX disposable syringe also contains in aqueous suspension with sodium citrate buffer, as w/v approximately 0.5% lecithin, 0.4% carboxymethylcellulose, 0.4% polyvinylpyrrolidone, 0.01% propylparaben and 0.09% methylparaben. Units benzathine penicillin G (as active ingredient); 300,000 units per cc.—10-cc. multi-dose vial. Each cc. also contains sodium citrate buffer, approximately 6 mg. lecithin, 3 mg. polyvinylpyrrolidone, 1 mg. carboxymethylcellulose, 0.5 mg. sorbitan monopalmitate, 0.5 mg. polyoxyethylene sorbitan monopalmitate, 0.14 mg. propylparaben and 1.2 mg. methylparaben.

Wyeth Laboratories
Philadelphia, Pa. 19101

*U.S. Dept. of Health, Education, and Welfare: VD Fact Sheet 1972. Publication No. (HSM) 73-8195.

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THE WESTERN
Journal of Medicine

Refer to: Mosso JA, Rand RW: Management of Parkinson's disease—Combined therapy with levodopa and thalamotomy. West J Med 122:1-6, Jan 1975

Management of Parkinson's Disease

Combined Therapy with Levodopa and Thalamotomy

JAMES A. MOSSO, MD, *Cincinnati,* and ROBERT W. RAND, PhD, MD, *Los Angeles*

An increasing number of parkinsonian patients in whom levodopa fails to relieve tremor are being referred for thalamotomy. The literature suggests that in as many as 50 percent of patients treated with levodopa, there is no relief of tremor because of refractoriness to the medication or intractable side effects which limit dosage. Thalamotomy abolishes contralateral tremor in 90 percent of patients, with an associated mortality rate of 1 to 2 percent and morbidity of 6 percent. The relative merits and complications of levodopa and thalamotomy were reviewed and a therapeutic regimen designed in which the two approaches to treatment are combined to most effectively deal with all the symptoms of parkinsonism.

SINCE THE INTRODUCTION of levodopa, few parkinsonian patients have been treated with surgical procedures in the thalamus. However, initial enthusiasm with levodopa therapy[1-3] has been tempered in the light of long-term studies involving large series of patients. The relative refractoriness of tremor to levodopa and intractable side effects of the medication combine to produce a large number of patients who remain disabled by tremor. This has been reflected in a growing number of referrals of levodopa "treatment failures" for thalamotomy. Our experience and a survey of the literature suggest a need to reappraise the roles of thalamic operation and levodopa in the treatment of parkinsonism.

From the Department of Surgery, Division of Neurosurgery, University of California, Los Angeles, School of Medicine.

Submitted July 1, 1974.

This project was supported in part by the Research Society for Parkinson's Disease and Movement Disorders, Inc., Los Angeles.

Reprint requests to: R. W. Rand, PhD, MD, Department of Surgery, Division of Neurosurgery, UCLA School of Medicine, Los Angeles, CA 90024.

Reports of Cases

Following are several representative case reports of parkinsonian patients referred by their neurologists for thalamotomy following an extensive trial of levodopa. In each case stereotaxic ventrolateral cryothalamotomy was done at the University of California, Los Angeles (UCLA) Hospital by one of us (RWR).

CASE 1. A 56-year-old, right-handed Caucasian man had an 11-year history of severe left-sided tremor and rigidity. A three-year course of levodopa, 4 grams per day, produced moderate symptomatic improvement, but resulted in the development of right-sided choreoathetoid movements. In spite of a reduction in the levodopa dose, dyskinesia increased in severity and prevented achievement of therapeutic levels. The patient had been unable to work for the past two years because of tremor, and progressive bradykinesia, dysarthria and dysphagia developed.

At the time of admission to UCLA Hospital in September of 1972, there was pronounced rigidity and constant resting tremor of the left arm and leg. Mild rigidity and intermittent tremor related to emotion were present on the right side. There were intermittent choreiform movements of the right shoulder, masklike facies, blunting of affect, dysarthria and slowing of gait. Mild hypertension (a blood pressure of 140/80 mm of mercury) was well controlled with medication.

Because the levodopa-induced dyskinesia prevented adequate control of tremor, the patient's neurologist referred him for consideration of thalamotomy. A right ventrolateral cryothalamotomy was done under local anesthesia and dexamethasone was used to limit postoperative edema. The procedure produced a 75 percent reduction in rigidity and abolished the tremor on the left. There were no postoperative neurologic deficits. The referring neurologist felt that the procedure had had an excellent result. Levodopa was to be continued at 1.5 grams per day for control of postural and right-sided symptoms. There was no change in the postoperative result on follow-up after 1½ years.

CASE 2. A 50-year-old, right-handed man, a minister, presented with a five-year history of Parkinson's disease manifest primarily as right-sided tremor and rigidity, with dysphagia and akinesia. A regimen of amantadine, trihexyphenidyl and levodopa, 4 grams per day, had resulted in major improvement in all symptoms except tremor, which remained severe and interfered severely with the patient's duties as a minister. Consequently, he was referred for thalamotomy.

On physical examination at admission, normal mental status and mild slowing of speech were noted, but there was no functional gait impairment. There was pronounced rigidity and constant tremor of right arm and leg, exacerbated by anxiety. No left-sided tremor or rigidity was present. Myerson and snout reflexes were positive.

A left ventrolateral thalamotomy was done in January 1971 under local anesthesia with postoperative administration of steroids. There were no postoperative complications. Rigidity was greatly reduced in the right arm and leg, and the patient became essentially free from tremor except for rare tremor during emotional stress. He was continued on levodopa, 1.5 grams per day, for control of bulbar symptoms. The tremor had not recurred at follow-up of three years.

CASE 3. Parkinson's disease first developed 15 years ago in a 61-year-old, right-handed man, a tailor. The disease was initially manifest as right-sided tremor and mild speech disturbance, unresponsive to medications available at the time. Left cryothalamotomy done in 1965 resulted in complete relief of the right-sided tremor, but two years later tremor involving the left arm and leg and severe gait disturbance developed. Treatment with levodopa was begun in 1970 and for several months the left-sided tremor was almost completely relieved, only to recur and become increasingly more severe in spite of maximal doses of levodopa in combination with amantadine. The tremor was disabling for the patient when dealing with customers in his tailor shop.

The patient was admitted to UCLA Hospital in September, 1971 for cryothalamotomy. On examination, mild deterioration of memory, slowing of speech, severe left arm and leg tremor (especially with anxiety) and moderate rigidity on the left side were noted. There was mild right-sided rigidity but no tremor. In addition, there was systolic hypertension (a blood pressure of 180/95 mm of mercury), asymptomatic mitral insufficiency and bilateral femoro-popilateral occlusive disease with absent lower extremity pulses.

Although hypertension and cardiovascular disease imposed increased risks, tremor was sufficiently disabling that cryothalamotomy was done. In spite of postoperative administration of dexamethasone, there was a transient period of mild hemiparesis and confusion. However, this cleared completely within five days and at the time of discharge the patient was free of tremor and there was pronounced improvement in left-sided rigidity. Administration of levodopa was not resumed postoperatively and the patient remains tremor-free 2½ years postoperatively.

CASE 4. A 66-year-old, right-handed housewife presented with an eight-year history of bilateral upper extremity tremor, more severe on the right side. Rigidity and bradykinesia were of minor significance. The tremor was unresponsive to available medical therapy, and in 1966 a left cryothalamotomy was done. There was complete and lasting relief of right-sided tremor, although the left arm and leg tremor became progressively more severe.

A trial of levodopa produced initial relief, but the tremor recurred and intractable nausea plus severe dystonic posturing of the left shoulder limited the dose of levodopa. Administration of

levodopa was tapered to reduce the side effects and eventually it had to be discontinued. Virtually all other available anti-parkinsonian drugs were tried and proved to be ineffective in treating the tremor.

The patient was admitted to UCLA Hospital in August, 1971 for thalamic operation. On physical examination, moderate rigidity and severe resting tremor involving the left arm and leg were seen, as well as dystonic posturing and occasional athetoid movements of the left wrist and hand. Minimal rigidity was present on the right, but tremor was not observed. Gait was festinating, affect was flattened and there was mild dementia and speech disturbance. In August, 1971 a right cryothalamotomy was done with excellent relief of tremor and no postoperative neurologic complications. When seen one year postoperatively, the patient was tremor-free; administration of levodopa was continued for control of gait disturbance.

CASE 5. A 64-year-old, right-handed woman, a cook, presented with three-year history of bilateral tremor, more prominent on the left, and slowing of gait. Initially, a good response was obtained with administration of trihexyphenidyl and amantadine, but relapse occurred. An 18-month trial of levodopa in maximal doses also produced only temporary remission. At the time of admission to hospital the patient was having great difficulty coping with her responsibilities as a cook in a local school because of tremor.

On physical examination in January, 1972, severe resting tremor, involving the left arm and leg, and moderate left-sided rigidity were noted. Occasional tremor was present on the right, particularly with emotion, but tone was only mildly increased. Gait was mildly impaired; speech and mental status were normal.

A right cryothalamotomy was done which completely relieved the contralateral tremor and greatly improved the rigidity. Truncal and bulbar involvement were minimal in this patient; therefore levodopa was discontinued postoperatively. At follow-up after 1½ years, the patient remains free from tremor.

Discussion

Now that sufficient time has elapsed to allow for critical reappraisal, the role of levodopa in the treatment of symptoms of Parkinson's disease may be reassessed and compared with the results of thalamotomy.

The therapeutic efficacy of levodopa in parkinsonism is well established. Generally, about two thirds of the patients treated with levodopa experience a pronounced symptomatic improvement,[4-8] but the remaining 30 percent show little or no benefit. Not all of the symptoms of parkinsonism are equally responsive. Although it is generally accepted that levodopa is the best agent available for the relief of bradykinesia and autonomic effects,[4-8] and is very effective in relieving rigidity, tremor is significantly less responsive, even at very high doses. Cotzias,[1] and Calne[5] in a review of the literature, note that levodopa is least effective in treatment of tremor. Langrall[6] in a study of 1,600 patients found an improvement in bradykinesia in 71 percent of the patients, and in rigidity in 70 percent. However, limb tremor was improved in 59 percent of the patients and an improvement in tremulous handwriting occurred in only 25 percent. Others have found that about one third of the 60 to 70 percent of patients in whom levodopa is effective in treating akinesia and rigidity show no improvement in tremor.[5,7,8] That is, less than half of the parkinsonian patients treated with levodopa alone had significant relief of tremor. As reported by Cotzias[1] and Markham,[7] and exemplified in the cases reported here, tremor which initially improved on levodopa therapy may recur and become refractory to long-term treatment.

Levodopa Side Effects

Side effects to therapeutic dosages are an important factor in limiting the overall effectiveness of levodopa. Side effects occurred with a frequency of 92 percent in Langrall's study of 1,600 patients.[6] In the majority of patients these reactions consisted of nausea, insomnia or confusion and were transient or, at worst, tolerable accompaniments to the therapeutic benefit. However, in as many as 30 to 50 percent of the patients side effects developed during the course of therapy which were serious enough to limit dosage or require cessation of treatment.[4-7]

Cardiac arrhythmias and postural hypotension have been related to levodopa in 7 to 30 percent of patients;[3,5,9] only a few fatalities have been reported.[5] Psychiatric side effects were seen in 20 to 30 percent of patients treated.[3,10-12] These included intellectual deterioration,[13] confusion, depression, psychosis and even occasional suicides.[3,10-12]

The problem of levodopa-induced involuntary movements was particularly disturbing, occurring

in 30 to 80 percent of patients.[3,5,7,8,14,15] These choreoathetoid or dystonic movements involving tongue, head or proximal limb muscles were generally dose-related. More bizarre motor disturbances have been reported in some patients on levodopa. Barbeau[15] found that 10 percent of patients developed an "akinesia parodoxica" in which a sudden hypotonia and hypotension rendered patients temporarily unable to move and which resulted in falls that often produced hip fractures. A peculiar "on-off" effect has been described that may produce abrupt swings from nearly complete remission to severe tremor, rigidity or choreoathetosis several times per day.[6,15] Transient unexplained comas lasting 1 to 24 hours have been reported.[3,16] These observations have prompted Barbeau to suggest that "after a while the metabolism of brain dopamine is modified" by levodopa.[15] Other alterations in brain chemistry have been reported.[17] Although yet to be established, there is some experimental evidence to suggest that levodopa induced dyskinesias may be related to cerebellar infarcts which have been demonstrated in animals on levodopa.[18] No significant toxic effects to the administration of levodopa have emerged to date, but minor abnormalities of laboratory values are found in a high percentage of patients.[5,6] There is increasing evidence that levodopa has metabolic side effects, including alterations in glucose metabolism and trophic hormone levels.[19]

Thus, troublesome side effects, unexplained refractory states and differential effectiveness are emerging as increasingly important limitations on the benefits derived from levodopa therapy. As a result, a growing number of patients are again being referred for thalamotomy to treat tremor and rigidity after levodopa has failed to produce satisfactory results.

Ventrolateral Thalamotomy

The value of ventrolateral thalamotomy in Parkinson's disease has been well documented since 1955. When the thalamic lesion is confined to the ventrolateral nucleus, immediate and lasting relief of contralateral tremor and, to a lesser extent, rigidity occurs in 70 to 90 percent of patients, depending on the criteria for patient selection.[20-23] In a series reported by Cooper,[20] in which he analyzed the results of 1,001 cryogenic thalamotomies done in 1963, tremor was completely relieved in 90.6 percent of patients, and improved in an additional 9 percent; there was no significant return of tremor in a mean follow-up of ten months. Ojemann and Ward[24] have shown that the improvement in tremor remained stable in 40 percent of patients with follow-ups as long as ten years, while disease in the opposite limbs and trunk continued to progress (the long-term efficacy of levodopa is yet to be established). Contralateral rigidity is 75 to 100 percent improved in two thirds of patients.[20-23]

The patients most likely to have excellent relief of tremor and rigidity with thalamotomy are those in whom involvement is primarily unilateral, with little bradykinesia, dysarthria or autonomic symptoms.[20,22] However, more than half of the patients with severe bilateral symptoms, including autonomic and bulbar dysfunction, can expect pronounced improvement in contralateral tremor and rigidity following thalamotomy.[22]

Bradykinesia generally does not respond to thalamotomy, although Ojemann and Ward[24] report some element of improvement in bradykinesia manifest as finger dexterity in 70 percent of their patients. Bulbar and autonomic symptoms of parkinsonism are essentially unaffected by thalamotomy.

The risks of stereotaxic thalamotomy have progressively decreased with the refinements of technique and experience in case selection of the past decade.[25] Overall mortality rates in large series are now less than 2 percent.[21-23,25-27] Death directly attributable to the procedure is usually a result of intracerebral hemorrhage, and occurs in 0.6 percent of patients.[20] The risk of fatal hemorrhage appears to be related to the degree of cerebral arteriosclerosis, as the mortality rate is zero in patients under 50 years of age, but increases to 1.9 percent by age 70 years, and 7.4 percent in patients with hypertension.[20] Systolic hypertension which is not readily controllable with medication is not considered a contraindication to stereotactic surgery. The remainder of the postoperative deaths are related to the effects of pulmonary emboli, myocardial infarcts and the like.

Postoperative Neurologic Complications

The most common postoperative neurologic complications have been imbalance, confusion and mental changes, speech disturbance and hemiparesis. In a review of the literature, Cooper[26] found that these complications occur in 5 to 20 percent of operations, but they are generally transient effects in the immediate postoperative period. Permanent neurologic complications following unilateral operations occur with a fre-

quency of 2 to 6 percent.[26,27] The age of the patient, the severity of the parkinsonism, the presence of other medical diseases and the surgical technique (including the number of lesions) appear to be the most important factors in the morbidity resulting from thalamic surgery.[25] The risk of speech disturbance is increased with dominant hemisphere lesions, and may be as high as 5 to 33 percent with bilateral stereotactic operation.[20,22,24,28,29]

Two technical developments have notably diminished the frequency of neurologic complications. Cryogenic stereotactic probes enable the surgeon to examine the patient for desired relief of tremor, as well as avoidance of complications, while the thalamic target is cooled under local anesthesia. If undesirable neurologic effects are produced, the probe is rewarmed immediately with completely reversible results. The use of dexamethasone in the immediate postoperative period greatly diminishes the incidence and severity of transient neurologic deficits that result from the edema surrounding the thalamic cryogenic lesion.

Hoehn and Yahr[30] have reported a study of the natural history of Parkinson's disease in 802 patients. They found tremor was the most common presenting symptom. In spite of control of tremor with thalamotomy and medications other than levodopa, the disease, as manifest by autonomic and bulbar effects and intellectual deterioration, continued to progress. After five years, one quarter of the patients were disabled or dead and after 10 to 14 years, 80 percent were disabled or dead. The principal causes for increased mortality, which was three times greater than the norm, were pneumonia and urinary infections as complications of the disease. The mortality associated with the disease thus must be weighed against the risks involved in thalamotomy or levodopa therapy. It is yet to be determined whether levodopa, through improvement in akinesia and autonomic effects, may alter the mortality and disability pattern of parkinsonism.

Therapeutic Regimen

With these considerations in mind it seems reasonable to propose the following regimen in the treatment of parkinsonian symptoms. In the majority of patients who present initially with a combination of bilateral rigidity, bradykinesia and tremor, a trial of levodopa and other medications is indicated for a period of 12 to 18 months. Of these patients, a group will emerge in whom tremor is not improved by levodopa. This group will be composed of the patients in whom therapy is limited by intractable side effects, and the patients in whom tremor shows little response to levodopa. According to the literature, this may amount to more than half of those treated with levodopa.[4-8] These patients should then be considered for thalamotomy by weighing the functional disability created by the unrelieved tremor and rigidity against the factors which may substantially increase surgical risk. Following thalamotomy, it is expected that the patients will continue to require levodopa for management of akinesia, autonomic symptoms and unilateral limb involvement. As reported by Hughes et al[32] in a double blind study, and confirmed by others,[11,33] patients who have had thalamotomies show no difference in the response of parkinsonian symptoms to levodopa than do those patients who have not had previous thalamotomy. Indeed, there appears to be a beneficial effect in that there is a lower incidence of levodopa induced dyskinesias following thalamotomy.[31]

Early in the course of parkinsonism, tremor is the most prominent symptom.[30] In a small group of patients, the disease may appear self-limited to tremor and rigidity of one or two limbs.[24,31] In these patients, if tremor is not relieved soon after achieving therapeutic dosage of levodopa, thalamotomy may be more strongly recommended. This is the group of young parkinsonian patients in whom the risks of thalamotomy are lowest, and in whom relief of tremor can be predicted in 90 percent. Many of these patients, of course, will eventually develop tremor and rigidity involving the opposite limbs. Bilateral staged thalamotomies involve additional risks, but can be done safely in well-selected patients (Case 4). For those patients who progress to akinesia and autonomic disorders, levodopa will again be required.

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Current Status of the Treatment of Syphilis

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Penicillin remains the treatment of choice for syphilis, with sustained low blood levels curing virtually all patients having early syphilis and halting disease progression in most patients with symptomatic syphilis. Tetracycline, erythromycin or cephalothin yields similar cure rates for patients with early syphilis who are allergic to penicillin. The efficacy of non-penicillin regimens for the treatment of late syphilis is uncertain. Results of Venereal Disease Research Laboratory (VDRL) or other reagin tests should become negative or remain at very low titer following adequate therapy, although results of Treponema pallidum immobilization (TPI) and fluorescent treponemal antibody-absorbed (FTA-ABS) tests often remain positive.

PENICILLIN, introduced for the treatment of syphilis in 1943,[1] is the drug of choice for the treatment of all stages of the disease. Treponema pallidum is one of the most penicillin-sensitive micro-organisms known and all available evidence suggests that its original sensitivity has not diminished.

A penicillin blood level of 0.03 units per ml is at least ten times that required for experimental inhibition of T. pallidum.[2] The longer the duration of infection, the longer the therapy needed for cure.[3] In very early syphilis, when there are few organisms, transient penicillinemia may be curative. It has recently been shown that a single dose of 2.4 million units of aqueous procaine penicillin G, which produces a blood level greater than 0.03 units per ml for 24 hours, cures incubating seronegative syphilis.[4] A penicillin level of 0.03 units per ml must be sustained for seven to ten days to cure primary and secondary syphilis, while three to four weeks is required for patients with tertiary syphilis.[5]

Because of the necessity for relatively low but sustained penicillinemia, the development of long-acting preparations greatly simplified the treatment of syphilis. A 300,000 unit dose of benzathine penicillin G (Bicillin®) gives 0.03 units per ml blood levels for seven days and the 2.4 million unit dose gives these blood levels for three to four weeks.[6,7] It is therefore possible to treat primary and secondary syphilis with a single injection of 2.4 million units of Bicillin, which is the recommended therapy for primary and secondary syphilis in the United States. In latent syphilis when no spinal fluid examination is done and in tertiary syphilis, a total dose of 9 million units of Bicillin divided over a three-week period is recommended. Any penicillin which produces comparable blood levels of comparable duration can be used. There is no evidence that increasing the dose or duration of

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penicillin therapy above these recommendations improves clinical or serological results.[5]

Recent advances in the treatment of syphilis include the first comprehensive review of the long-term effects of penicillin therapy, and further evaluations of alternate therapy for syphilis in patients allergic to penicillin. New serologic tests which facilitate diagnosis will not be considered here.

Long-term Results of Penicillin Therapy

For an excellent review of the long-term results of penicillin therapy, the reader is referred to a recent supplement of the Bulletin of the World Health Organization published in 1972.[5] In this series, collected from the published literature, 97 percent of 1,381 persons with seronegative primary syphilis were clinically well and serologically negative two to ten years after treatment. The 3 percent "failures" were considered to have been reinfected. Among 1,030 persons with primary seroreactive syphilis, 93 to 100 percent became serologically non-reactive as determined by lipoidal antigen tests. Most or all of the failures were again believed to be due to reinfection. Although reagin tests nearly always reverted to negative, approximately 30 percent of the patients studied retained positive Treponema pallidum immobilization (TPI) after nine years. Similar results were found in 783 patients with secondary syphilis: over 98 percent became seronegative to reagin tests, but nearly 40 percent had persistently positive TPI tests. Most of an additional 2,458 patients with early or early latent syphilis became serologically nonreactive to reagin tests within ten months, and all did so within two years, but only 50 to 70 percent reverted to TPI nonreactivity within the observation period.[8] The absence of a wave of late syphilis following the peak of infectious syphilis occurring during World War II is attributed to the use of penicillin.

The treatment of late latent syphilis appears to be curative although reagin nonreactivity five years after treatment occurs in only 20 to 30 percent of cases, a result comparable with the spontaneous seroconversion achieved in Oslo patients without treatment.[9] Few become nonreactive to TPI tests.[10] In the 469 reported cases of late latent syphilis followed for up to 12 years after treatment with 5 to 15 million units of penicillin, no progression of late latent to late symptomatic syphilis was documented.[5] Further, late symptomatic syphilis has not been reported in any patient who received adequate penicillin therapy before the development of symptomatic syphilis.

The benefit of treatment in patients with established cardiovascular syphilis is difficult to ascertain both because the prognosis depends on the extent of tissue damage at the beginning of treatment[11] and some patients remain asymptomatic and survive to old age without treatment.[12] Nevertheless, most of the 1,168 patients with cardiovascular syphilis reported by 13 investigators were said to have had reduced symptoms or prolongation of life or both.[5] Although aortic regurgitation may first appear after completion of treatment, data are insufficient to attribute this progression to penicillin therapy (therapeutic paradox) or its failure.[13]

Similarly, the benefit of treatment for symptomatic neurosyphilis varies with the amount of disease at the onset of therapy. Most of the 6,902 patients followed for up to 12 years were said to show clinical improvement and a return to or toward normal in the cerebrospinal fluid.[5] However, Wilner and Brody[13] reported that in 25 of 64 patients with general paresis surviving at least ten years after penicillin therapy, new neurologic signs developed. Efficacy is better documented in the treatment of primary optic atrophy, which invariably progresses to blindness without treatment.[8] Although therapy does not reverse changes that have already occurred, early treatment may halt progression and preserve vision in at least 50 percent of cases.[5]

Less than 30 percent of the 8,189 patients with late symptomatic syphilis became seronegative by reagin tests five years after treatment.[5] Most had persistently positive TPI tests. The ability of the host to immobilize treponemes could reflect continued antigenic stimulus by persistent spirochetes. The finding of treponemes in the eyes, brains and lymph nodes of patients treated with penicillin is of great interest but it is as yet without proven clinical significance.[15-17]

Penicillin treatment of the mother earlier than the fourth month of pregnancy prevents congenital syphilis. Later treatment of the mother—actually transplacental treatment of the child—usually prevents congenital syphilis. A most striking failure was the recently reported fatal case in an infant whose mother was treated with penicillin before delivery and who also received massive doses of penicillin after birth.[18] There was no experimental evidence that the treponeme in this

case was resistant to penicillin, and the reason for the treatment failure is unknown.

In congenital syphilis of less than two years' duration, penicillin treatment results in clinical and serological cure in almost all cases, although the conversion to seronegativity may take at least six months.[5] Treatment given for congenital syphilis of more than two years' duration probably prevents later sequelae but the rate of seronegativity is much lower.

The only documented complication of penicillin therapy of syphilis in non-allergic patients is the Jarisch-Herxheimer reaction. This febrile reaction occurs in 50 to 95 percent of patients treated for primary or secondary syphilis, and is seen in early seronegative syphilis as well.[5,10,19,20] The reaction does not appear to be dose-related and there is no evidence that starting with small doses of penicillin or giving bismuth beforehand reduces the frequency of reactions.[19] The Herxheimer reaction is rare in patients with late symptomatic syphilis,[20] but it is here that it is most feared. Aortitis as a complication of therapy is frequently alluded to in the literature, although only seven "fatal Herxheimer reactions" were included in 1,168 patients treated for cardiovascular syphilis.[5] It is difficult to assess the role of treatment in this outcome because sudden deaths occur without therapy and narrowing of the orifice of the coronary arteries has been reported in at least 25 percent of cases in which autopsy was done.[21] Data are inconclusive regarding corticosteroid prophylaxis of Herxheimer reaction during the treatment of late symptomatic syphilis, but many venerologists recommend that steroids be given with antibiotics to patients who have optic or auditory disease.

Alternate Therapy

The incidence of penicillin allergy as reported in venereal disease clinics has not changed in the past 20 years in the United States.[22] Although such reactions are rarely fatal, a history of a penicillin reaction is nearly always a contraindication to the use of the drug for the treatment of syphilis. The efficacy of other antibiotics for treatment of infectious syphilis is relatively well documented, but there is less information about chemotherapy of late syphilis with drugs other than penicillin.[23]

The largest single experience has been with chloramphenicol. As reported by the World Health Organization group, 286 patients with early syphilis received from 10 to 48 grams over a period of six to thirty-six days; 197 became serologically negative within two years and another 18 had reductions in reagin titer.[5] Only nine patients (3 percent) were considered to have had treatment failure. None of nine pregnant patients treated with 20 grams of chloramphenicol over a period of ten days delivered syphilitic babies. In another study 15 patients, five of them pregnant, were cured of early syphilis following 60 mg of chloramphenicol per kilogram of body weight for six to eight days.[24] Dark-field negativity and serologic conversion may not be as prompt as that seen with penicillin but the final results appear to be comparable. The risk of chloramphenicol-associated aplastic anemia precludes its use for the treatment of syphilis except in unusual cases.

Erythromycin is also effective treatment for early syphilis. A study by the United States Department of Health, Education, and Welfare showed that 15 to 20 grams of erythromycin estolate given over ten days failed in 9.2 percent of 261 patients with seronegative primary syphilis and in 4.4 percent of 224 patients with seroreactive secondary syphilis.[25] (The higher failure rate in seronegative syphilis may be explained by reinfection.) Erythromycin estolate does cause occasional hepatotoxicity in adults. Erythromycin base is unassociated with hepatotoxicity but affords lower blood levels. According to Schroeter et al,[26] a 12-month failure rate of 26.8 percent followed the 20 gram schedule. By increasing the dose to 30 grams over the ten-day period, the failure rate at 12 months was reduced to 10.9 percent. Dose efficacy may be related to the weight of the patient, as no definite relapses were noted following the 20 gram dose in 34 patients whose average weight was 120 pounds.[27] Although erythromycin crosses the placental barrier poorly, it has been used successfully for the treatment of pregnant patients with syphilis.[24] Failures have been reported, however, the best documented case being that of South et al,[28] who reported fatal congenital syphilis in an infant whose mother was treated with 15 grams of erythromycin estolate given over a ten-day period two months before delivery.

The treatment of early syphilis with the tetracyclines was reviewed by the WHO group: 163 patients were treated with chlortetracycline, oxytetracycline or tetracycline in doses of from 4 to 70 grams given over periods of seven to twenty-one days.[5] All of the treatment failures occurred in one group of 101 patients receiving 70 grams of chlortetracycline over 11 days.[29] Some of the failures may have been due to variation in drug

potency, as the study was done early in the commercial development of the agent. Other failures were possibly due to the conditions of a concomitant study, apparently in the same patients, demonstrating reduced blood levels when the antibiotic was taken with milk or aluminum-hydroxide-gel. In a more recent study, 30 grams of tetracycline given over a ten-day period cured 90.8 percent of patients with early syphilis.[26] At 24 months, the proportion of cases in which retreatment was necessary (12.7 percent) was not significantly different from that following penicillin (10.7 percent). Most of patients retreated were believed to have reinfection. Moderate to severe gastrointestinal side-effects of tetracycline occurred in 2.3 percent of patients, compared with 11 percent of those treated with erythromycin. Tetracycline is probably the best alternative to penicillin for the treatment of infectious syphilis. At least ten cases in which pregnant women delivered normal babies following tetracycline treatment have been reported,[24-29] and no documented case in which tetracycline failed to prevent congenital syphilis appears in the literature. Nevertheless, because of its effect on the fetus and the danger of hepatotoxicity in pregnant women, tetracycline is a poor choice for the treatment of pregnant patients.

The cephalosporins are the only other adequately tested alternative for the treatment of patients with early syphilis. Duncan and Knox[30] reported that cephalexin, 250 mg twice a day for 15 days, failed in half of 18 patients with early syphilis; although a decrease in titer and healing of primary lesions occurred promptly, secondary syphilis or other evidence of recurrence developed later. On the other hand, possible cephaloridine failures have been reported in only three of at least 45 patients with early syphilis who received 5 to 26 grams over six to fourteen days.[30-35] There were no treatment failures in ten pregnant patients with syphilis. Cephaloridine, which crosses the placenta to yield levels approximately 60 percent of those in maternal blood, may prove to be the treatment of choice for syphilis complicating pregnancy in penicillin-allergic patients.[36] It should be recalled, however, that some allergic patients are also allergic to cephaloridine; and serious reactions, including anaphylaxis, have been reported.[37]

Follow-up

Follow-up of patients treated for early syphilis is based mainly on the use of serologic tests.[38] As was previously indicated, a negative reagin test should be expected in patients with syphilis of less than two years' duration; failure to achieve this result suggests either reinfection or relapse, and is an indication for retreatment. The Venereal Disease Research Laboratory (VDRL) or equivalent test usually reverts to normal within six months to a year in patients treated with penicillin, but may take up to two years in patients apparently adequately treated with other antibiotics. In any case, the titer should be low or falling. In syphilis of more than two years' duration an increasing proportion of patients never become reagin-negative. In such patients titers should be low or decreasing after treatment, but there is no objective endpoint indicative of cure. For this reason it may be advisable to retreat pregnant women who have positive reaction to serologic tests.

The fluorescent treponemal antibody-absorbed (FTA-ABS) test is the most sensitive test available for the diagnosis of all stages of syphilis, but is less useful as a test of cure.[38] Like the TPI test, which it has largely replaced, the FTA-ABS test may remain positive in one-third of patients treated for early seropositive syphilis, and there is at present no evidence to suggest that further treatment is indicated or that symptomatic syphilis will later develop in such patients. Approximately 98 percent of patients with treated late syphilis retain a positive reaction to FTA-ABS test.

In past years it has been recommended that a cerebrospinal fluid examination be done approximately a year after treatment of early syphilis as a further test of cure. This is probably not necessary for seronegative patients who have received an adequate course of penicillin and is no longer recommended by the U.S. Public Health Service; in England all of 1,379 patients who had a spinal fluid examination at least one year after treatment of early syphilis had normal findings.[39] Because less information is available about the prognosis of patients treated with drugs other than penicillin, such patients should have a spinal fluid examination a year after treatment as part of their follow-up.

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Psychological Antecedents to Conception Among Abortion Seekers

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At a university hospital, 642 women seeking induced abortion for an unwanted pregnancy were surveyed before the procedure regarding their perception of what psychological and behavioral factors, if any, played a role in their becoming pregnant: 35 percent said they had had intercourse during what they believed was a "safe period"; 33 percent believed that they had experienced a contraceptive failure; 29 percent indicated fear of side effects influenced their use of a contraceptive method; 27 percent and 21 percent, respectively, indicated that they had thought pregnancy "couldn't happen to me" or had "put the thought of pregnancy out of my mind." The women's responses indicated that a number of additional attitudes, beliefs, and behaviors were also important and that for any individual woman at least three or four factors had often combined in a dynamic sequence to greatly increase her risk of pregnancy. The implications of the findings for educational and counseling programs are discussed.

AMONG THE CONSEQUENCES of unwanted pregnancies, three are most salient: the effects of being unwanted upon the child himself; the effects of an unwanted child upon the parents and the family; and the effects of unwanted children upon society at large, especially with respect to overpopulation, resource utilization and the overall quality of life. In spite of the problematic and undesirable nature of the effects, there is considerable evidence that in the United States we are far from having mastered the psychological and behavioral antecedents to conception.[1] For example, recent survey data indicate that in intact marriages, on the average, one in five children is unwanted.[2] Adding to this the growing incidence of therapeutic abortion in states with liberalized abortion laws[3] and the rising illegitimacy rate,[4] it is clear that unwanted pregnancies, by whatever criteria one wants to measure their occurrence, are a major public health problem.

In order to better understand what psychological factors might play a role in the occurrence of pregnancies which were perceived as unwanted

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after conception, a pilot investigation was carried out in a large group of women seeking induced abortions. These women were surveyed regarding their own perceptions of the psychological and behavioral factors which led to their unwanted pregnancies. Given its survey nature, attention was focused in this study upon consciously accessible psychological factors such as the attitudes, expectations and beliefs of respondents with regard to their own sexuality, their fertility (ability to conceive), their use of contraception and the meaning of pregnancy to them. Within this large focus of concern, special emphasis was placed upon the women's antecedent use of contraception.

Methods

Concurrent with passage by the California Legislature in 1967 of a therapeutic abortion law which allowed the interruption of pregnancy to preserve the physical and mental health of the mother, there occurred a liberalization of physician and community attitudes toward the procedure. Local custom determined that an abortion could be obtained for very broadly interpreted mental health reasons upon the recommendation of two psychiatrists. Since a large majority of local psychiatrists readily approved women for abortion (the refusal rate was a fraction of 1 percent), therapeutic abortion became available to virtually all women living in the urban and suburban centers who desired it and sought it out. As a result, there was a pronounced increase in the number of abortions done throughout the state. These developments resulted in the initiation of a one-year medical and demographic survey of all abortion patients at Stanford University Hospital, beginning in October, 1970. The data which constitute the subject of this report were collected within the context of this survey over a six-month period, during which time 692 women received abortions at the hospital. Each woman was asked to complete a short questionnaire (the Contraceptive and Sexual Attitude Questionnaire) and to answer a brief set of questions regarding her personal history and contraceptive practice. If she agreed, the woman signed a consent form, completed the questionnaire and was interviewed for ten to fifteen minutes.

Three quarters of the respondents were private patients, and one quarter were clinic patients. The private patients were all contacted the day they came to the hospital to be admitted for the procedure. Most of the clinic patients were also interviewed at that time, although approximately 25 percent of them were interviewed one day before their admission when they attended the obstetrics clinic for a preoperative examination. Approximately half of all the respondents expressed interest in the study and were glad to have someone with whom to talk before the procedure. A large majority of the remaining respondents appeared to accept the study and to participate in a straightforward way without showing either enthusiasm or resistance. Those respondents who were too anxious or upset to discuss personal matters or to complete the questionnaire were either excluded from the study or were given the option of keeping the questionnaire, completing it within the next few days and mailing it back to the investigator. Of the 692 eligible subjects, 7 percent were unable to participate in the study or refused to do so. Of the 642 subjects who did participate in the study, 2 percent mailed the questionnaire back rather than complete it at the time of the interview.

There were three interviewers ranging in age from 21 to 32. All three were white, two were unmarried and one was married. Initially, each was given a broad range of basic information on sexuality, contraception and abortion. At the same time each was trained regarding interview techniques. Their ongoing interview behavior was then monitored through daily individual supervision as needed and regular weekly group supervision.

The Contraceptive and Sexual Attitude Questionnaire consists of 53 items describing attitudes, beliefs and expectations relevant to the contraceptive and sexual behavior of women. The respondent completes the questionnaire by checking each item suggesting a factor which played a role in her becoming pregnant. These items were selected using information from many interviews with women applying for therapeutic abortion or attending a gynecological clinic for contraception or pregnancy testing. The items were carefully worded to conform as closely as possible to the way these women expressed themselves when describing the psychological and behavioral conditions under which they became pregnant or feared they might become pregnant. After the questionnaire had been pretested and used in the study for two months, five more items were added as a result of comments and suggestions made by women who had already participated in the survey.

More complete evaluation of some of the respondents' actual use of contraception was ac-

complished by interviewing the second half of the sample (328 subjects) more intensively regarding the details of their use of contraception at the time of conception. This interview also followed administration of the Contraceptive and Sexual Attitude Questionnaire, and focused upon the degree to which a respondent's pregnancy appeared to result from the failure of an effectively used contraceptive method. Criteria for effective use were based on a standard contraceptive text.[5]

Results

The study sample was characterized by demographic and personal history characteristics: 96.5 percent of the respondents lived in California; 36.9 percent were 19 years of age or under, 33.1 percent were 20 to 24, 15.9 percent were 25 to 29 and 14.0 percent were 30 or above; 61.4 percent of the respondents were never married, 21.2 percent were currently married and 17.4 percent were formerly married; 81.2 percent of the respondents were white, 10.7 percent were black and 8 percent were of other racial-ethnic backgrounds; 36.9 percent of the respondents were Protestant, 21.5 percent were Roman Catholic, 5.8 percent were of other religious affiliations and 35.8 percent had no affiliation; 23.4 percent of the respondents had less than a high-school education, 32.3 percent had achieved a high-school diploma, 30.9 percent had one to three years of college and 13.5 percent had at least a college degree. The sample's previous reproductive history was characterized: 55 percent of the respondents had no living children, 13 percent had one, 11 percent had two, and 11 percent had three or more; 18 percent of the respondents had had at least one previous out-of-wedlock conception and 9 percent of the respondents had had at least one previous induced abortion. All of the respondents were asked what method of contraception they used at or around the time of conception: 54 percent indicated that they had used nothing and the remainder indicated that they had used rhythm (14 percent), foam (9 percent), withdrawal (5 percent), oral contraception (5 percent), diaphragm (5 percent), intrauterine contraceptive device (IUD) (3 percent), condom (3 percent) or some other method (2 percent).

The responses of the respondents to the Contraceptive and Sexual Attitude Questionnaire are shown in Table 1. In this table, the items are listed in order of decreasing frequency. Low-frequency items are shown, as well as high-frequency ones, in order to demonstrate the importance of the psychological and behavioral variables relative to each other. The mean number of items checked by all respondents was 3.5, with a range of 1 (most commonly Item 2) to 12.

Because of the frequency with which respondents indicated that their pregnancy resulted from a contraceptive failure, it was of interest to consider to what extent checking Item 2 coincided with a contraceptive failure as judged by the interviewers. For the 328 respondents who completed the questionnaire and were interviewed regarding their actual use of contraception at the time of conception, the following data were obtained: 20 (8 percent) of the 239 respondents who did not check Item 2 were judged to have had a contraceptive failure and 21 (24 percent) of the 89 respondents who did check Item 2 were judged not to have had a contraceptive failure. Of the 21 false positives, 15 respondents (71 percent) were using rhythm or oral contraception at the time of conception in a way which they felt was adequate, but which the interviewer (using a stricter set of criteria regarding effective use of contraception) judged to be inadequate. In general, these stricter criteria involved a narrower definition of the "safe period" and a stricter definition of what counts as adequate pill-taking.

In order to examine further the relationships between psychological factors and contraceptive behavior, a chi-square analysis was done on the relationship between contraception at the time of conception and the response to each questionnaire item. The data for those items with a significant chi-square analysis are presented in Table 2.

Discussion

With respect to age, marital status and racial-ethnic status, the study sample is very similar to the population receiving therapeutic abortions during the same time period in the State of California as a whole.[6] Compared with a much larger national population receiving therapeutic abortions during this same time period, the age distribution for the study sample is also very similar.[3] Thus, the findings in this pilot investigation may cautiously be generalized to many populations of women in the United States who are at risk for an unwanted pregnancy and favorably disposed toward therapeutic abortion as a problem-solving technique.

The distribution of responses to the Contraceptive and Sexual Attitude Questionnaire supplements the clinical observations made by others in

TABLE 1.—*Percentage of respondents in the study group who checked each Contraceptive and Sexual Attitude Questionnaire item, indicating it played a role in the occurrence of their unwanted pregnancy. (N=642)*

Item Number	*Questionnaire Item*	*Percent of Respondents Checking Item*
1.	I thought it was during the safe period	35
2.	I took precautions but the contraceptive method didn't work	33
3.	I was afraid of the side effects of certain contraceptives	29
4.	I thought it couldn't happen to me	27
5.	I put the possibility of pregnancy out of my mind	21
6.	I didn't think pregnancy was likely because I had intercourse so infrequently	14
7.	I didn't think I would get pregnant because I have often had intercourse without precautions and have never gotten pregnant before	14
8.	I realized that if I did get pregnant I could probably get an abortion	13
9.	I decided to take a chance and count on good luck	12
10.	I had planned not to have any more intercourse for a while	11
11.	I just never got around to getting contraception	10
12.	I got carried away before I could think about contraception	9
13.	I halfway wanted to get pregnant	8
14.	He was supposed to withdraw but he didn't	8
15.	I was embarrassed or afraid to see a doctor about contraception	8
16.	I didn't like deliberately planning for the possibility of intercourse	8
17.	I loved him and nothing else mattered	8
18.	I knew I might get pregnant but that uncertainty didn't concern me very much	6
19.	I was in the process of beginning a new contraceptive method*	6
20.	I didn't think I was fertile*	6
21.	I was afraid someone would find out if I tried to get a contraceptive*	6
22.	I assumed that he would take some kind of precautions	5
23.	I felt that having intercourse on that occasion was worth the chance of pregnancy	5
24.	My judgment was affected by alcohol	5
25.	I wanted to prove my love by taking a chance	4
26.	I was embarrassed or afraid to talk to him about contraception	3
27.	I sort of liked putting myself in a risky situation	3
28.	I felt a contraceptive would interfere with the natural expression of love	3
29.	At the time I wanted to get pregnant	3
30.	I really didn't care that much whether I got pregnant	3
31.	He wanted to have a baby even though I didn't	3
32.	I couldn't say no even though there wasn't any available contraception	3
33.	My judgment was affected by a drug (marijuana, LSD, etc.)	3
34.	I was forced against my will to have intercourse	3
35.	I thought that using contraception would make it harder to say no in the future	3
36.	He assured me he was sterile or that he could not make me pregnant	3
37.	I didn't know how to get contraception*	2
38.	He didn't want me to use contraception	2
39.	I was confused by my doctor about contraception	2
40.	I felt that all available contraceptives were distasteful	2
41.	The doctor made it hard for me to get the contraceptive I wanted	2
42.	I thought that if I got pregnant we would get married	2
43.	We couldn't agree what kind of contraceptive method to use	2
44.	I didn't think any contraceptive really worked	1
45.	I was trying to hurt or punish myself	1
46.	I wanted to prove that I was fertile	1
47.	I felt it was wrong and against my beliefs to use contraceptives	1
48.	I thought that using a contraceptive would change how he felt about me	1
49.	I wasn't able to take precautions because he was in such a hurry	1
50.	I thought that if I got pregnant it would improve our marriage	1
51.	My usual contraceptive method was not available*	1
52.	I only felt right if there was a chance of pregnancy	0
53.	I wanted to get back at someone by getting pregnant	0

*These five items were added after questionnaire distribution began. The N of subsample for these five =373.

TABLE 2.—*Percentage of respondents saying "yes" to questionnaire items, by all respondents and by respondents using different methods of contraception at time of conception.*

Item Number	*Contraceptive and Sexual Attitude Questionnaire Item*	*All Respondents*	*No Contraception*	*Withdrawal*	*Rhythm*	*Condom*	*Pill*	*Foam*	*Diaphragm*	*IUD*	*Significance of Row Chi Square*
1.	Thought during safe period	35	32	40	76	42	22	23	10	0	.001
2.	Method didn't work	33	7	37	39	74	75	83	87	100	.001
3.	Afraid of side effects	29	29	30	35	21	9	44	27	22	.1
4.	Couldn't happen to me	27	31	30	25	26	25	23	7	6	.1
5.	Put possibility out of mind	21	28	13	17	21	22	10	7	6	.01
6.	Intercourse infrequently	14	17	20	22	21	0	3	0	0	.01
7.	Never gotten pregnant before	14	20	13	13	0	6	7	3	0	.01
10.	Planned no more intercourse	11	15	20	11	5	3	5	3	0	.1
11.	Never got around to getting contraception	10	12	30	13	16	0	2	0	0	.001
12.	Got carried away	9	13	7	5	5	3	2	3	0	.1
14.	He was supposed to withdraw	8	11	30	4	0	0	3	0	0	.001
15.	Embarrassed or afraid to see MD	8	8	20	11	11	6	2	0	0	.01
19.	Beginning new method	6	3	0	10	0	21	13	0	0	.1
	N of sample:	642	346	30	92	18	32	59	30	19	

a nonsystematic way[7] by suggesting the relative importance of different psychological antecedents for unwanted pregnancies which are aborted. However, in the interpretation of each questionnaire item, it must be kept in mind that the respondent was asked to check all those items which played some role in her becoming pregnant, and that most respondents checked three or more items. In the infrequent instances when respondents checked only one item, it usually was Item 2, which deals with actual contraceptive failure. Thus, none of the psychological factors suggested by questionnaire items should be viewed as operating alone. Rather they should be thought of as operating in conjunction with several other factors. The importance of such a multifactorial approach can be appreciated by recognizing that obtaining and successfully using a contraceptive method almost always involves a complicated sequence of psychological and behavioral events,[1] which tend to occur in a stepwise sequence: deciding to be sexually active, or acknowledging to oneself that one is sexually active; recognizing the possibility of pregnancy and the implications that this would have for oneself and for others; thinking about, talking about and planning methods for preventing pregnancy; acquiring a contraceptive method for personal use; keeping it available in situations where one might decide to have intercourse; deciding what to do when it is not available and using it regularly. Each item of the Contraceptive and Sexual Attitude Questionnaire relates to failure at one or more of the steps in this psychological and behavioral sequence. In checking multiple items, the typical respondent is therefore indicating what combination of step failures led to her unwanted pregnancy.

The most frequently checked item in Table 2 indicates that the respondents felt sexual intercourse was taking place during a nonfertile period in the menstrual cycle. On the basis of interviews with a subsample of respondents, however, it can be said that only a small minority of the women who checked this item were actually well informed on the facts of ovulation and the correct use of the method of periodic abstinence. Rather, most respondents appeared to be using the concept of the "safe period" as a way of rationalizing the safety of a particular act of sexual intercourse after they were in a situation where they wanted to have intercourse but had no suitable contraceptive method available, and, in some cases, after unprotected intercourse had already taken place. It was this consistent finding that led the author's research assistants to coin the term "retrospective rhythm."

The second most frequently checked item on the questionnaire indicates that a third of the respondents felt conception resulted from a contraceptive failure. If this figure is adjusted for the 24 percent of those respondents checking Item 2 who were judged as false positives on the basis of the interview, there still remains approximately 25 percent of the total sample who accurately perceive themselves as becoming pregnant because of a contraceptive method failure. Therefore, it

appears that for a large group of abortion seekers psychological factors have not played a primary role in their unwanted pregnancies.

The third most frequently checked item indicates that the respondent was afraid of certain contraceptive method side effects. In the study sample, the methods toward which most of this concern was directed were oral contraception and the IUD Unfortunately, these are the two most effective methods available. During the interviews this fear and concern appeared to operate at three levels: by influencing whether the woman obtained contraception, which contraceptive method was chosen and how the contraceptive method was used once it was obtained.

The fourth and fifth most frequently checked items indicate that the respondents excluded thoughts about becoming pregnant from consciousness. In and of itself, such exclusion may be either an adaptive or maladaptive mental mechanism. For example, a small group of respondents checked both Item 2 and one or both of Items 4 and 5, indicating that they took reasonable contraceptive precautions and that this enabled them to suppress the thought or fear of pregnancy. However, a majority of the respondents who checked Items 4 or 5 were practicing maladaptive denial, in that they excluded thoughts or fears of pregnancy at the same time that they were taking inadequate contraceptive precautions.

A number of the questionnaire items were checked with an intermediate frequency of between 8 percent and 14 percent. Item 6 suggests a poor comprehension of the actual risks of pregnancy. This appears to be based on the common fallacy that low-frequency exposure to an outcome which is only probabilistic will prevent the occurrence of that outcome. Items 7 and 20 indicate that the respondent believed she was subfertile (in demographic usage, subfecund). This was most commonly true among the adolescents and the women undergoing menopause. As the author has discussed elsewhere,[8] women appear to be more vulnerable to an unwanted pregnancy during the periods of adolescent and menopausal subfertility because of their failure to learn contraceptive vigilance in the former or their relaxation of an acquired vigilance in the latter. Item 8 suggests that the perceived availability of abortion may have decreased the strength of contraceptive vigilance in a significant fraction of women in the sample and thus affected the adequacy of their contraceptive practice or the extent to which they took risks. A willingness to take risks was very directly suggested by Item 9. For many of the women interviewed, checking this item meant that the respondent had decided on a particular occasion that intercourse was "worth the chance of pregnancy."

Items 10, 11 and 16 each suggest a somewhat different type of problem with future planning. Item 10 suggests difficulty in following through on a plan to abstain from further sexual intercourse. There were two basic situations which tended to facilitate the making of such a plan: breakup with or separation from a long-standing sexual partner and an episode of sexual involvement about which the woman felt considerable remorse or guilt. In both situations, the woman's reactive psychological state led her to temporarily reject the thought of further sexual activity. This resulted in her being contraceptively unprepared when she did resume her sexual activity. Item 11 suggests an inability to plan for sexual intercourse through the prior securing of contraception. This inability may represent an inhibition of planning because of negative feelings about sexuality or contraception, or it may simply represent a lack of future orientation. Finally, Item 16 suggests an inhibition of planning for intercourse because of the deliberateness and the implicit psychological initiative which such planning involves. On the one hand, deliberateness implies a lack of spontaneity. This consideration is also reflected in the relatively low-frequency Item 28. On the other hand, initiative implies assertiveness, even aggressiveness. Such an implication runs strongly counter to traditional views of female sexuality.

Poor sexual impulse control is suggested by Item 12. This type of difficulty has the most serious implication for respondents using coitus-dependent contraceptive methods because of the requirement that the user temporarily inhibit ongoing sexual activity in order to apply the method. Items 13 and 29 both indicate a conscious wish to become pregnant. While the latter suggests a strong, active wish, the former is phrased in a way which suggests a more passive, semiconscious or ambivalent wish. It is noteworthy that the active wish to become pregnant was relatively unimportant among all the psychological factors. The passive wish, on the other hand, was almost three times as important. It was our observation that this passive form of the wish to be pregnant was more

commonly expressed in the woman's fantasy rather than translated directly into action and probably affected the chances of conception by slightly modifying the adequacy of each step in her contraceptive behavior sequence.

Item 14 indicates that the respondent perceived the pregnancy as resulting from her sexual partner's failure to withdraw. Many women reported difficulty discussing their sexual feelings and contraceptive preferences with their partners. But more is reflected in this item than poor communication. It also provides some measure of the woman's tendency to project the blame for the pregnancy onto her partner. In addition, since the man sometimes misled her about withdrawal or simply failed to follow through on his intention, this item also reflects the woman's misplaced trust in her partner. Item 15 indicates an embarrassment on the part of the respondent in seeing a doctor about contraception. This consideration was especially prominent among the younger respondents in the sample, especially those still living at home and limited to their family doctor, or those living in a small town or on a college campus where confidentiality was a major consideration. Item 17 indicates an absorption in the present and in the respondent's current heterosexual relationship. This consideration was also more prevalent in the younger members of the sample. Finally, Items 24 and 33, one or the other of which was checked by 8 percent of the respondents, indicate poor judgment regarding contraception and pregnancy resulting from the use of alcohol or other psychoactive compounds.

Some of the infrequently checked items are noteworthy because they are traditionally assumed to be relatively important factors in the occurrence of an unwanted pregnancy. Items 42, 50 and 53 all imply the manipulative use of a pregnancy or a child to influence others. It seems likely that Items 42 and 50 represent factors which may actually be more significant for all pregnancies in a population than just for those pregnancies which are aborted since it will be primarily when the manipulation fails that the woman seeks an abortion. Item 46 implies the respondent's use of conception to reassure herself regarding her own reproductive ability. While this factor is a frequently mentioned motive for premarital pregnancy in nulliparous women, its low frequency in Table 1 suggests either that, in fact, it is relatively unimportant or that it operates largely outside of the awareness of the woman herself. Items 37 and 47 represent frequently discussed societal and moral obstacles to the use of contraception. Their low frequency in this sample almost certainly reflects the ready availability and general acceptance of contraception in the geographic area from which the sample was drawn.

Table 2 provides some interesting information regarding the behavioral problems associated with specific contraceptive methods. In that table, the first column represent the entire study sample and indicates the percentage of all respondents saying "yes" to the particular questionnaire item listed on the left-hand side of the table. The next eight columns present data from the eight subgroups of respondents grouped with reference to contraceptive use at the time of conception. The subgroups are arranged according to the adequacy of each subgroup's contraceptive practice, with the least effective contraceptors (no contraception) on the left, and the most effective (IUD) on the right. In between, the subgroups are arranged, from left to right, to show increasing adequacy of contraception as determined by the percentage of each subgroup's respondents who indicated they had a method failure (by checking Item 2). The general appropriateness of this ordering of subgroups is confirmed by examining the percentage of each subgroup checking the other questionnaire items which reflect the adequacy of contraceptive practice at the time of conception, such as the denial, planning or impulsivity items.

The item profile of IUD-using respondents is clearly the most favorable, although that of the diaphragm-users is very similar. The item profile of foam-users is also similar, although this subgroup tends to be higher on rationalization (Item 1) and denial (Items 4 and 5). Respondents using oral contraception are similar to the foam-users. However, they have two item response patterns that tend to differentiate them from all other contraceptors: they are far the least fearful of side effects and they are most likely to experience an unwanted pregnancy while beginning a new method. The first of these patterns is not unexpected, since the Pill-users have selected the very method about which there has been the most public discussion of problematic side effects. The second pattern reflects two facts especially relevant to oral contraception. First, there is often a considerable delay between the decision to obtain oral contraception and actual procurement of the

medication. A doctor or a clinic must be identified, an appointment must be made, an examination must be obtained from a physician and often a prescription must be filled before the medication is in hand. Second, the transition period during which a woman changes from some other contraceptive method (or no method) to oral contraception has certain inherent ambiguities regarding when to begin administration and when to consider that protection has begun. Some patients who are instructed to wait until after their next menstrual period before beginning administration become pregnant in the interim. Others who mistakenly believe they are protected from conception with the first pill also become pregnant.

The item profile for the condom-users is similar to those of the Pill- and foam-users except for their responses to Items 1, 6, 11 and 15, which together suggest a set of resistances to planning contraception which probably fosters more frequent reliance on their male partner for contraception. Except for the noncontraceptors, the users of withdrawal and rhythm are the least adequate contraceptor groups. Their item profiles are very similar except for their responses to Items 1 and 14, which relate very specifically to the respective methods.

When interpreting the data in Table 2, it must be kept in mind that the psychological factors associated with a particular contraceptor subgroup cannot be attributed to all users of that method. The respondents in each contraceptor subgroup were selected out of the large pool of users of that method by virtue of their failure to prevent conception. However, because of this selective process, the psychological factors associated with particular methods in the data of this investigation suggest behavioral dispositions in a potential contraceptor which may predispose her to failure should she use that particular method. The nature and importance of such interactions between a user's psychological characteristics on the one hand and the set of behaviors required by each contraceptive method on the other have been discussed at greater length by the author in other writings.[9,10]

Conclusion

The results of this survey of women seeking abortion support the proposition that many different psychological factors play an antecedent role in the occurrence of unwanted pregnancy, although in a quarter of the cases psychological factors appeared not to have played a fundamental role. Each of the more important psychological factors in this survey appears to operate at one point or at different points in the complex behavioral sequence which leads to effective contraception. If sex education and counseling programs and birth control or family planning clinic programs could communicate more about these factors, the frequency of unwanted pregnancy might be considerably reduced. Such a goal might be accomplished if educators, counselors and clinicians gave special emphasis to certain material: the facts and risks of both rhythm and withdrawal as methods of contraception; the major side effects and undesired consequences of both contraception and pregnancy; the psychological mechanisms of suppression and denial, with their adaptive and maladaptive functions; the statistics of conception following random and infrequent sexual intercourse; the types and implications of subfertility; the sequence of behaviors necessary for adequate contraceptive use; the psychological factors which predispose persons to the ineffective use of each contraceptive method; motivations for sexual intercourse and the medical, psychological and ethical aspects of induced abortion.

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This symposium is from a Special Endocrine Conference held at Harbor General Hospital, January 1974

Complications of Oral Contraceptive Agents

—A Symposium

Action and Efficacy of Systemic Contraceptive Agents, and Introduction of Complications

RONALD S. SWERDLOFF, MD*

THE NEED FOR population control has been emphasized repeatedly by numerous social and biological scientists over the past few decades. The almost geometrical population growth in the world is shown in Chart 1. This chart, prepared only a few years ago, allowed for the projected further expansion (dashed line) if the population is not further controlled.[1] The gravity of the situation can be seen from the following calculations. In 1969 the world population stood at 3.6 billion people. It was estimated then that in the next 31 years the world population would more than double and by the year 2040 would reach 14 billion, or a quadrupling of the population in 70 years.[2]

This projected growth has raised great concern. Two important questions have been raised: (1) Will there be adequate foodstuff to maintain life (of whatever quality), and (2) what happens to people when they are overcrowded even if nutrition is adequately maintained? The effect of the world population expansion on food supplies has been recently emphasized to us by the 1973 world food shortage and the resultant inflated food prices. Recently reported long-term studies on overcrowding of mice housed in a predator-free, germ-free, controlled environment with ample food may well predict the potential risk to man. In these studies, after a sharp population expansion, social behavior deteriorated badly and ultimately stopped and the colony became extinct two and a half years later.

With the problem thus defined, we can look at the present state of the art of birth control. While there are many ways of limiting reproduction—such as sexual abstinence (rhythm method), physical obstruction to fertilization (condoms and diaphragms), interference with implantation by local means (intrauterine device)—this symposium will

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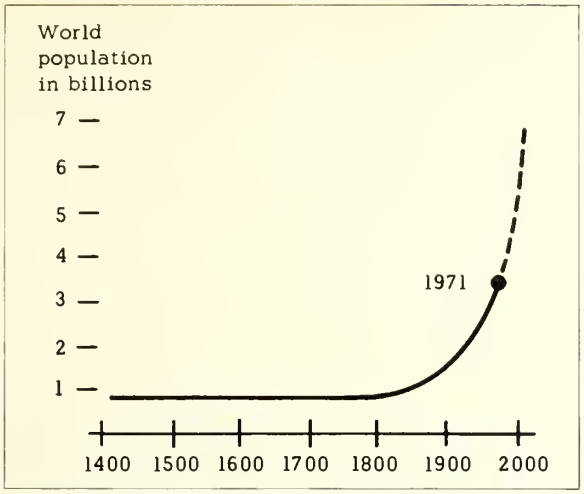

Chart 1.—Long term changes in world population. The dashed line represents the projected population as of 1971. (Reproduced by permission from Odell WD: Reproductive biology, **In** Odell WD, Moyer DL: Physiology of Reproduction. St. Louis, Mo., The C. V. Mosby Company, 1971)

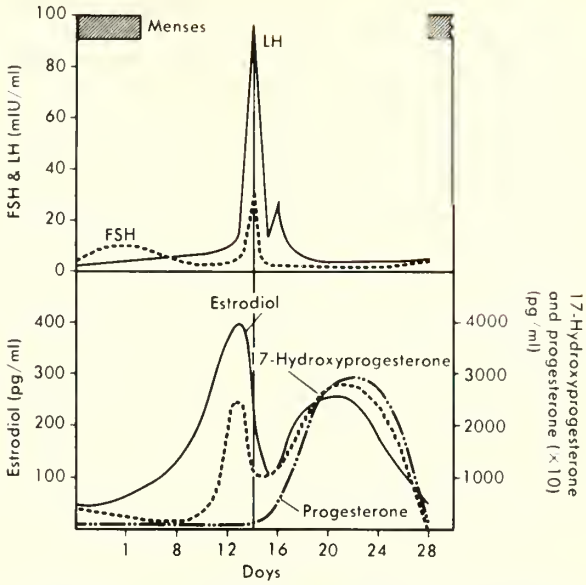

Chart 2.—Schematic representation of the fluctuations in serum luteinizing hormone (LH), follicle stimulating hormone (FSH), progesterone, 17-hydroxy-progesterone, and estradiol during the normal menstrual cycle in women. Note that both estradiol and 17-hydroxy-progesterone rise before the LH-FSH ovulation surge. In order to show progesterone and 17-hydroxyprogesterone on the same scale, progesterone concentrations were divided by 10; that is, they are actually ten times greater than shown. (pg/ml = picograms per milliliter) (Reproduced by permission from Odell WD, Moyer DL: Physiology of Reproduction. St. Louis, Missouri, The C. V. Mosby Company, 1971)

limit itself to a discussion of systemic contraceptives, their mechanisms of action, and their effectiveness and side effects.

Hormonal Control of Ovulation

The hormonal events responsible for ovulation are complex and only recently becoming fully understood. Chart 2 represents the changes in serum levels of two pituitary hormones, luteinizing hormone (LH) and follicle stimulating hormone (FSH), and three gonadal steroids, estradiol (E_2), progesterone (P), and 17α hydroxyprogesterone (17P) during a normal menstrual cycle.

FSH rises early in the cycle. This rise in the presence of permissive concentrations of serum LH stimulates ovarian follicular growth and maturation which in turn results in increasing secretion of estradiol and 17α hydroxyprogesterone. When estradiol reaches a critical level, it acts on the hypothalamic-pituitary axis to stimulate the release of a large amount of LH and, to a lesser extent, FSH. These gonadotropins induce the mature follicle to release its ovum and a corpus luteum is formed. Progesterone, now secreted in increasing amounts, and estrogen, which has remained high, act to inhibit the secretion of LH and FSH and prepare the uterus for the potential implantation of a fertilized egg. In time, the ovarian secretion of estradiol and progesterone diminishes and in the absence of pregnancy, uterine mucosal sloughing occurs resulting in menses. The fall in estrogen and progesterone then acts to stimulate the hypothalamic-pituitary axis to secrete FSH and a new cycle is begun. The interruption of this cycle is one of the important mechanisms by which many of the steroid contraceptive agents work.

Following ovulation the ovum is transported down the fallopian tube where it is fertilized by a sperm. The sperm responsible for fertilization is one of millions deposited into the vagina; the deposited sperm migrates through the cervical mucus into the uterus and ultimately into the fallopian tube. The fertilized ovum continues to move down the fallopian tube and into the uterus which has been prepared for implantation by the proper balance of ovarian steroids. Alterations of cervical mucus, impaired or accelerated tubal transport of the ovum, or lack of proper uterine preparedness for implantation are all factors by which systemic agents could have important contraceptive effects.

Systemic Contraceptive Agents

Table 1 lists the five types of systemic contraceptive agents which have received adequate clinical trials and are available for use in the United

TABLE 1.—*Types of Systemic Contraceptive Agents*

- Combined estrogen-progestogen pill
- Sequential estrogen-progestogen pill
- "Mini" progestogen pill
- Injectable long-acting contraceptive
- "Morning after" pill

States. The first four types of agents have been advocated for chronic preventative use in women with frequent coital exposure. In contrast, the post-coital agent has potential practical use only in women with infrequent or unpredicted exposure.

Chemical Structure of Drugs Used as Contraceptive Agents

The substances used in contraceptive drugs can be generally divided into estrogenic and progestational agents. The estrogens are usually synthetic steroid substances (Chart 3B) but in the case of the post-coital pill may be of a non-steroidal variety such as stilbestrol. The progestational agents are either 19-nortestosterone derivatives (Chart 3C) or are 17 acetoxy-progesterone derivatives (Chart 3D). These estrogenic and progestational agents are representatives of the compounds that are used either alone or in a combination in the various types of contraceptive drugs. Their metabolic effects are obviously different and their pathogenic role in the specific side-effects seen with contraceptives differ.

Combined Estrogen Plus Progestogen Agents

Combined estrogen and progestogen agents have been used clinically for almost 20 years. They consist of an estrogen combined with a progestogen in various combinations (Table 2).[3] The single pill is given daily from the fourth day after onset of menses to day 24 of the cycle, is discontinued to allow withdrawal bleeding, and then is reinstated.

The mechanism of action of these agents can be seen in Chart 4. With the use of continued agents, the complex hormonal changes seen in Chart 2 are blocked. The early FSH rise does not occur, a mid-cycle LH surge is absent, and ovulation is prevented.[4] Evidence that the inhibition may occur at the hypothalamic level includes the demonstration that an LH surge can be produced in female rats administered contraceptive preparations following the injection of the hypothalamic releasing hormone, LRH.[5]

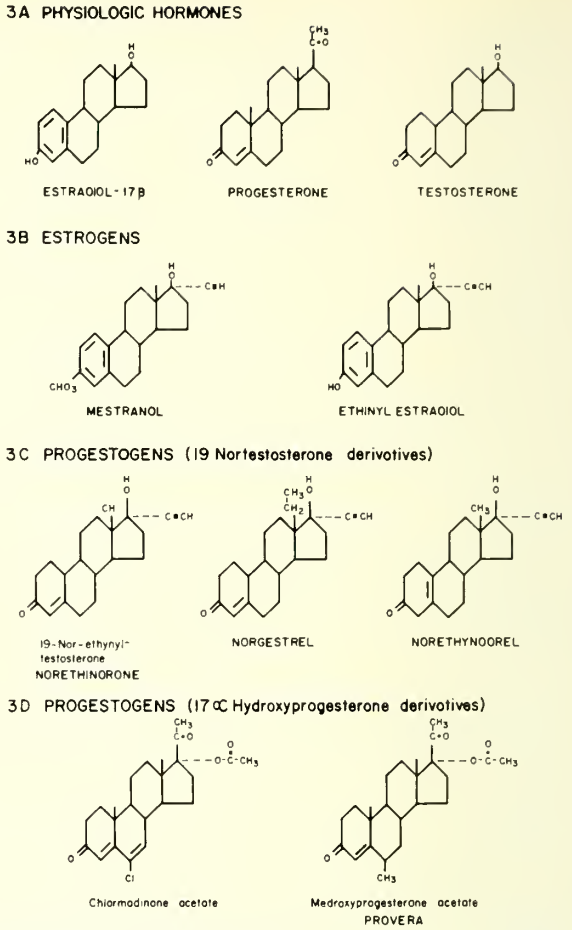

Chart 3.—Chemical structure of drugs used as contraceptive agents. Contraceptive agents may include one or more steroid substances.

The effectiveness of combined contraceptives when taken faithfully has been remarkable, resulting in a pregnancy rate of only 1 per 1,000 women years.[3]

Sequential Contraceptives

Sequential contraceptives, also containing estrogen and progestogen agents, differ from the combined contraceptives in that the estrogen medication is given alone for the first 15 to 20 days of the cycle, then is followed by combined estrogen and progestogen treatment for a short time.

The estrogen component of these drugs (see Table 1) also inhibits ovulation, but results in a different pattern of serum LH and FSH than that seen with the combined drugs[4] (Chart 5). In this study, ethinyl estradiol given alone inhibited FSH but resulted in multiple spikes of LH. It has been presumed that the follicle did not mature properly and therefore was not responsive to the LH surges which might occur close to the usual time.

TABLE 2.—*Various Combinations of Progestogen and Estrogen in Commercially Available Contraceptive Agents**

COMBINATION	*Progestogen : Estrogen*	*Trade Names (Manufacturers)*	*Administration*
Ethynodiol diacetate ...	1 mg : 100 μg mestranol	Ovulen (Searle)	From 5th through 24th or 25th day of cycle or 21 days of treatment followed by 7 days during which no pills are taken or iron containing 75 mg ferrous fumarate tablets are taken. The number 20 or 28 following the trade name indicates number of tablets in package.
	1 mg : 50 μg ethinyl estradiol	Demulen (Searle)	
Norethindrone	10 mg : 60 μg mestranol	Norinyl 10 mg (Syntex) Ortho-Novum 10 mg (Ortho)	
	2 mg : 100 μg mestranol	Norinyl 2 mg (Syntex) Ortho-Novum 2 mg (Ortho)	
	1 mg : 80 μg mestranol	Norinyl+80 (Syntex) Ortho-Novum 1/80 (Ortho)	
	1 mg : 50 μg mestranol	Norinyl+50 (Syntex) Ortho-Novum 1/50 (Ortho)	
Norethindrone acetate ..	2.5 mg : 50 μg ethinyl estradiol	Norlestrin 2.5 mg (Parke, Davis)	
	1 mg : 50 μg ethinyl estradiol	Norlestrin 1 mg (Parke, Davis)	
Norethynodrel	9.85 mg : 150 μg mestranol	Enovid 10 mg (Searle)	
	5 mg : 75 μg mestranol	Enovid 5 mg (Searle)	
	2.5 mg : 100 μg mestranol	Enovid-E (Searle)	
Norgestrel	0.5 mg : 50 μg ethinyl estradiol	Ovral (Wyeth)	
SEQUENTIAL			
Dimethisterone	25 mg : 100 μg ethinyl estradiol	Oracon (Mead Johnson)	Ethinyl estradiol for 16 days, then dimethisterone plus ethinyl estradiol for 5 days.
Norethindrone	2 mg : 80 μg mestranol	Norquen (Syntex)	Mestranol for 14 days, then norethindrone plus mestranol for 6 days.

*Adapted from JAMA 214:2318, Dec 28, 1970.

In addition, a direct effect of estrogen and progestogen drugs on the endometrium results in impaired implantation of a fertilized ovum and provides protection above and beyond their anti-ovulatory role.

While the sequential drugs were attractive initially because of the attempt to simulate a normal hormonal milieu more closely, they have proved to be less effective than the combined drugs, allowing a pregnancy rate of approximately 5 per 1,000 women years, a five-fold increase over the combined drugs under omission-free conditions.

The Mini Pill

In the early 1960's, studies began on the possibility of using progestational compounds in smaller and smaller doses (without the addition of estrogen compounds) as a means of conception control. As the controversies over estrogen and thromboembolism grew, the potential attractiveness of this approach increased.

A number of 19-nortestosterone and 17 acetoxy-progesterone derivations used in microgram doses have been referred to as "mini pills." They are administered once daily in a continuous fashion. Theoretically, menstrual bleeding occurs on a regular basis simulating normal menses.

The pregnancy rate from these compounds varies from 0 to 16.4 pregnancies per 1,000 women years (Table 3),[6] depending on which series is examined. The average pregnancy rate appears to be about 3 per 1,000 women years, a figure which is acceptable, but significantly higher than that for the combined contraceptives.

The mechanisms of action of these compounds are complex, but inhibition of sperm penetration through cervical mucus seems to be one of the most important.[2,7,8] Ovulation suppression appears to be an inconsistent action of the microdoses of these drugs,[6,9,10] and irregular multiple and non-predictable LH peaks may be seen in women taking them.[10,11]

Other described effects of these drugs include impaired function of the corpus luteal secretion of steroids, possible altered tubal transport and impaired uterine receptiveness to implantation. The major clinical problems other than the increased pregnancy rate from these compounds is the high

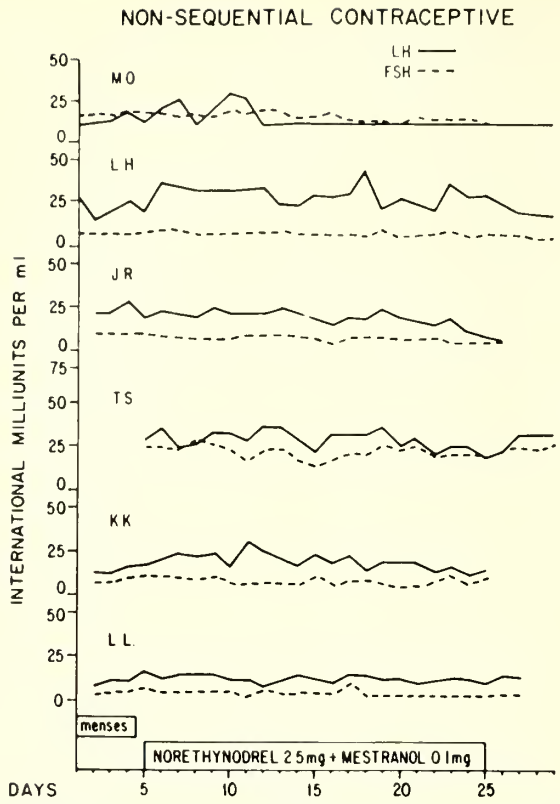

Chart 4.—Serum LH and FSH concentration measured daily in 6 eugonadal women receiving the combination of norethynodrel, 2.5 mg, and mestranol, 0.1 mg, from day 5 to day 25 of the menstrual cycle. (Reproduced by permission from Swerdloff RS, Odell WD: J Clin Endocrinol 29:157, 1969)

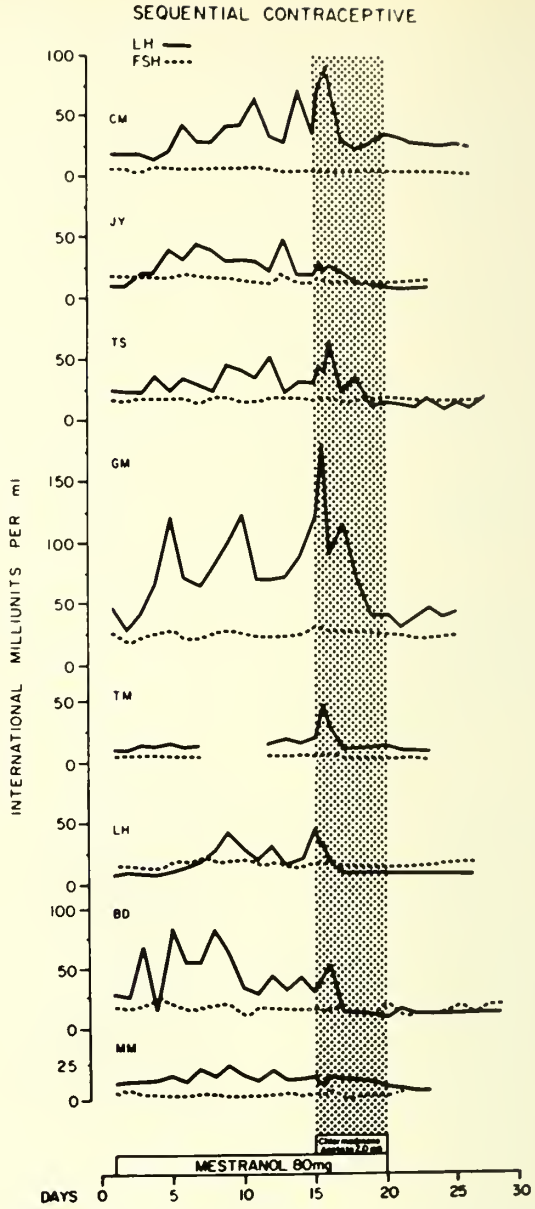

Chart 5.—Daily serum LH and FSH concentrations in eight women receiving a sequential type contraceptive. (Reproduced by permission from Swerdloff RS, Odell WD: J Clin Endocrinol 29:157, 1969)

frequency of intermenstrual bleeding and prolonged amenorrhea while taking them.

Long-Acting Hormonal Contraceptives

Long-acting systemic contraceptive agents have been evaluated in both an oral and an intramuscular form. The parenteral preparations have received the greatest consideration. These have consisted of two types: (1) a high dose of the depo form of progestogen—for example, depo-medroxyprogesterone acetate (DMPA)—and (2) combined depo progestogen and estrogen.

DMPA has been investigated most. The effectiveness of this drug has been demonstrated by Mishell,[12] who found no pregnancies in 5,399 patient months of experience on a regimen of 150 mg of DMPA intramuscularly every three months. Two problems occur with this regimen. Irregular vaginal bleeding occurs frequently during the first six months of therapy. This bleeding decreases with time and amenorrhea is usually seen by one year. Amenorrhea may persist after discontinuation of the drugs. Scutchfield et al[13] found 23 percent of patients had amenorrhea at 12 months post-treatment while Gardner and Mishell[14] found that nearly all had resumed menses; become pregnant or had a secretory endometrium by 18 months post-therapy.

The mechanism of action of DMPA may include effects on sperm penetration and uterine receptiveness, but inhibition of ovulation appears to be regularly observed. Cyclic LH and FSH discharge is

TABLE 3.—*Pregnancy Rate from Low-Dose Progestogens**

Investigator	*Drug*	*Dose (mg)*	*Number of Cycles*	*Pregnancy Rate in 100 Woman Years*
Martinez-Manautou et al (1967)	Chlormadinone acetate	0.5	25,158	3.6
Butler and Hill (1969)	Chlormadinone acetate	0.5	1,642	9.5
Espagno (1969)	Chlormadinone acetate	0.5	710	9.5
Jeppson and Kullander (1969)	Chlormadinone acetate	0.5	2,021	1.8
Howard et al (1969)	Chlormadinone acetate	0.5	2,080	8.6
Larsson-Cohn (1970)	Chlormadinone acetate	0.5	1,909	3.2
Bernstein and Seward (1972)	Chlormadinone acetate	0.5	3,199	4.5
Foss et al (1968)	Norgestrel	0.05	2,250	3.2
Satterthwaite et al (1969)	Megestrol acetate	0.50	1,319	16.4
Larsson-Cohn (1970)	Norethindrone	0.50	1,600	0.8
Larsson-Cohn (1970)	Norethindrone	0.40	1,299	0
Larsson-Cohn (1970)	Norethindrone	0.30	2,395	1.5
Rubio et al (1972)	Quingesterol	0.30	2,489	1.9

*Reprinted by permission from Larsson-Cohn U: Acta Endocrinologica 64:Supplement No. 144, 1970.

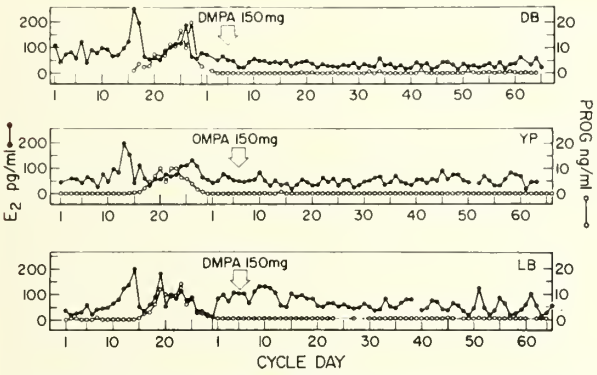

Chart 6.—Daily serum estradiol and progesterone levels in three women for one control cycle and two months after receiving an injection of 150 mg of DMPA (arrow). (Reproduced by permission from Mishell DR Jr, Kharma KM, Thorneycroft IH, et al: Am J Obstet Gynecol 113: 372, 1972)

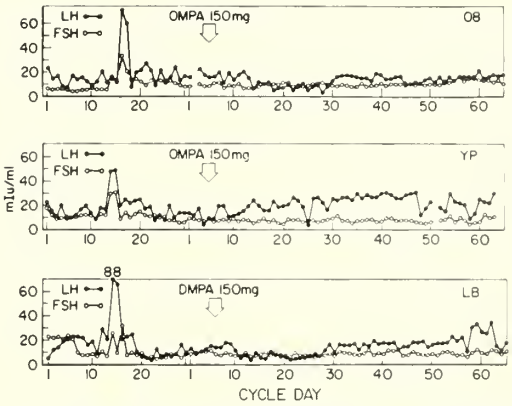

Chart 7.—Daily serum LH and FSH levels in the same three women as Chart 6. (Reproduced by permission from Mishell DR Jr, Kharma KM, Thorneycroft IH, et al: Am J Obstet Gynecol 113:372, 1972)

inhibited and estradiol levels remain in the early follicular range (Charts 6 and 7).

Another approach for depo progestogens has been the use of silastic and silicone rubber implants of the progestogen megestrol acetate. The pregnancy rate in a study by Coutinho et al[15] was estimated to be between 1 and 3 per 1,000 women years, depending on their analysis.

Injectable depo progestogen combined with either estradiol enanthate or depo estradiol cypionate has received some trials but appears to have little advantage over DMPA alone.[16,17]

In summary, the long-acting depo preparations, none of which have been released by the Federal Drug Administration for use as contraceptives, would appear to be effective means of preventing childbirth. They suffer from the disadvantages of irregular bleeding and the reservations about persistent post-treatment amenorrhea which occurs in some patients. If they are ever released for general use, they would appear to have the greatest possible role in patients who for various reasons are unreliable pill takers.

The "Morning After" Pill

Post-coital contraception has received considerable attention in both the lay and the scientific press. Both estrogens (diethyl stilbestrol) and progestogens (norethindrone) have been considered for this purpose. One synthetic estrogen, diethyl stilbestrol (DES) has received clinical trial. Twenty-five milligrams twice daily for five days begun within 72 hours of sexual exposure resulted in no pregnancies in 1,000 women of childbearing age.[18] The side-effects consisted mainly of nausea and vomiting, in about 13 percent of the patients. The mechanism of action is thought to be disturbance to tubal transport of the ovum, resulting in

TABLE 4.—*Some of the Side-Effects, Real or Purported, Ascribed to Estrogen-containing Contraceptive Agents*

Minor
Weight gain and edema
Nausea, vomiting and change in bowel habits
Vaginal spotting
Migraine headaches
Increased serum globulins-confusion in hormone measurement
Chloasma
Hirsutism
More Serious
Hypertension
Thrombophlebitis and embolic disease
Intrinsic vascular changes
Cerebral vascular occlusive disease
Impaired carbohydrate tolerance
Unknown risk of cervical neoplasia
Liver disease
Hyperlipidemia
Post treatment amenorrhea and galactorrhea

the premature presence of the ovum in an unprepared uterus.[19] This form of contraception has little attractiveness for use in women with frequent coital exposure. It does have great potential, however, for the women with infrequent or unpredicted exposure, including cases of criminal rape.

One progestogen, norethindrone, in large doses was found to provide low protection as a post-coital contraceptive.[20]

Complications of Contraceptives

Whenever drugs are administered to healthy persons for experimental or prophylactic purposes, great concern is appropriately expressed about possible side-effects. When such drugs are administered to millions of people, even a low incidence of serious side-effects may become an important health problem; such is the case with the estrogen-containing contraceptives. These agents, initially demonstrated in animal or human trials to be remarkably safe, now, after almost two decades of use by patients, have been demonstrated to have many minor and a few, although unusual, serious side-effects.[21] Many of these real or purported side-effects are listed in Table 4.

The minor complications of vaginal spotting, edema, nausea, and chloasma are not uncommon. Migraine headaches can be a troubling problem in predisposed women. The migraine seems to be precipitated by the falling levels of steroids which occurs at the time of monthly discontinuation of therapy.

Estrogens have many metabolic effects on the liver. These effects will be discussed in detail later by Dr. Fisher.

Also seen in Table 4 are the more serious side-effects. An analysis of the role of contraceptive agents in the production of these complications will be presented in the following sections.

An Analysis of the Reported Association of Oral Contraceptives to Thromboembolic Disease

WILLIAM D. ODELL, MD, PhD*

Dr. Swerdloff has reviewed the mechanism of action and various types of oral contraceptives in present use. Oral contraceptives have become one of the commonest forms of contraceptive devices and millions of women throughout the world have been taking them for several months to many years. While the incidence of serious side-effects attributed to these drugs is low, some of them are life-threatening. If these side-effects are causally related to oral contraceptive treatment, then the total number of people affected will be very large. Thus, understanding the cause-and-effect relationship of side-effects should be thorough. At the outset it should be said that the possible statistical increase in life-threatening side-effects in women without predisposing factors is very low. We will attempt to put that in perspective later in this review.

Thromboembolic Disease

The initial studies in the United States reported that women receiving oral contraceptives were no more likely to have thrombophlebitis or embolic phenomena than were those not receiving oral contraceptives. For example, in 1963 the Food and Drug Administration of the United States reviewed more than 350 reports of thromboembolic diseases in women taking Enovid® (norethynodrel with mestranol).[22] They estimated that among white women taking Enovid the mortality from thromboembolic disease was 12.1 per million, whereas the comparable mortality in the general

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TABLE 5.—*Use of oral contraceptives by women who died of pulmonary embolism. Numbers expected from experience of control women of similar age and parity are shown in parentheses.*†

Predisposing Conditions	Number of Deaths Among: Users of Oral Contraceptives	Nonusers of Oral Contraceptives	All Women
Absent (class A)	16 (4.2)	10(21.8)	26
Present (class B)	9 (6.8)	40(42.2)	49*
Total (class A and B)	25(11.0)	50(64.0)	75

*Two patients whose contraceptive practice was unknown omitted from this category.

†Reprinted by permission from Inman and Vessey: Br Med J 2:193, 1968.

TABLE 6.—*Use of oral contraceptives by women who died of cerebral thrombosis. Numbers expected from experience of control women shown in parentheses.*†

Predisposing Conditions	Number of Deaths Among: Users of Oral Contraceptives	Nonusers of Oral Contraceptives	All Women
Absent (class A)	5(1.5)	5 (8.5)	10
Present (class B)	0(1.5)	16(14.5)	16*
Total (class A and B)	5(3.0)	21(23.0)	26

*One patient omitted from this category whose parity was unknown (nonuser).

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TABLE 7.—*Affected and control patients classified by use of oral contraceptives during month before onset of disease episode (or during month before hospital admission in case of patients undergoing elective operation). (Percentages shown in parentheses)**

Diagnostic Group	Number of Patients: Users of Oral Contraceptives	Nonusers of Oral Contraceptives	All Women
Thromboembolism	26(45)	32(55)	58(100)
Control	10 (9)	106(91)	116(100)
Both groups	36(21)	138(79)	174(100)

*Reprinted by permission from Vessey and Doll: Br Med J 2: 199, 1968.

population was 8.4 per million. They concluded that there was no significant increase in the risk of death from thromboembolic disease in women receiving Enovid but advised that further studies be performed. Further consideration revealed that healthy young women probably should have a lower incidence of thromboembolism than the entire population, which includes older age groups and persons with other predisposing factors. In 1966 the Food and Drug Administration stated that 5,000,000 women were taking oral contraceptives and that 85 deaths would have been expected from thromboembolic phenomena based upon the national mortality statistics.[23] However, only 13 deaths were reported in these women receiving oral contraceptives. Surprisingly, the same year the Committee on Safety of Drugs received reports of 19 deaths per 400,000 women receiving oral contraceptives and 10 of these 19 had no predisposing factors.[24]

In 1968 Inman and Vessey,[24] and Vessey and Doll[25] first reported studies which appeared to indicate that thromboembolic phenomena *might* be increased in women receiving oral contraceptives. Inman and Vessey[24] reviewed 309 deaths* reported to be caused by thromboembolic phenomena in the British Isles (Table 5). Seventy-seven of these patients had pulmonary thrombosis or embolus, 205 had coronary thrombosis or myocardial infarction and 27 had cerebral thrombosis or embolus. It is important to understand the investigators' method of control selection. They asked each physician who cared for one of the patients to go to the place in his records where that patient's chart would have been kept, and to move backwards or forwards from that position, selecting two, and later three or four women in the same age range. These patients were then located and interviewed for predisposing factors and oral contraceptive use. In this manner, 998 suitable controls were gathered and the percent of these control subjects taking oral contraceptives was obtained and related to the age of the patient and her parity. Note from Table 5 that the number of women receiving contraceptives in the group who had pulmonary embolism was greater[46] than that expected from the control groups.[32] In a similar manner, they studied the incidence of cerebral thrombosis and embolism (Table 6), and concluded that the incidence of these diseases is probably increased in women receiving oral contraceptives. The incidence of coronary thrombosis was not significantly greater and no firm conclusion was made. In a separate article, Vessey and Doll[25] in 1968 reviewed the data from 19 general hospitals, each of which had more than 300 beds, and identified patients admitted with deep vein thrombosis or pulmonary embolus. (It is to be noted that the first article[24] dealt with deaths, the second[25] with hospital admissions.) For each pa-

*344 deaths were reviewed, but 35 patients were eliminated from study for various reasons, such as the fact that they were postpartum.

TABLE 8.—*Relative Risks of Thromboembolism at Various Dose-Levels of Estrogen (Data for United Kingdom)**

	Mestranol Estrogen Dose (μg)				*Ethinyloestradiol Estrogen Dose (μg)*		*Number of Reports*
	150	100	75-80	50	100	50	
Fatal pulmonary embolism	6.0	3.3	2.1	1.2	2.2	1.0	59
Non-fatal pulmonary embolism	3.2	1.7	1.3	1.4	2.5	1.0	234
Deep venous thrombosis of lower limb	1.9	1.4	1.1	1.2	3.3	1.0	235
Other venous thrombosis of lower limb	1.9	1.3	1.3	2.1	1.8	1.0	252
All venous thrombosis	2.4	1.6	1.2	1.5	2.5	1.0	780
Cerebral thrombosis	3.9	1.4	0.8	0.6	..	1.0	79
Coronary thrombosis	3.0	1.4	0.3	1.3	2.1	1.0	61

*Reprinted by permission from Inman et al: Br Med J 2:203, 1970.

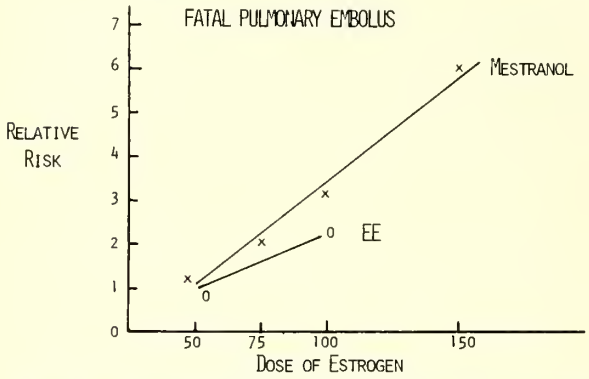

Chart 8.—Graph of the relative risk of fatal pulmonary embolus plotted against dose of estrogen in the oral contraceptive used. (Plotted from Inman WHW et al: Br Med J 2:203, 1970)

tient identified they obtained two control patients from the same hospital and selected those controls as patients admitted at the same time but having acute medical or surgical conditions, other than thromboembolic phenomena or admitted for elective operation. They found that 45 percent of the patients having thromboembolic disease were taking oral contraceptives but only 9 percent of the control patients were taking oral contraceptives (Table 7). There was again no significant difference in the patients who had coronary thrombosis or infarction. The investigators concluded (from this study design) that "risk of hospital admission for venous thromboembolism is about nine times greater in women taking oral contraceptives than in those who do not." Vessey and Doll[25] extrapolated these findings to the national population, calculating that 1 in every 2,000 women using oral contraceptives are admitted with idiopathic venous thromboembolism in comparison with about 1 in every 20,000 women not using them.

Most recently, Inman, Vessey, Westerholm and Engelund[26] attempted to relate the incidence of thromboembolic disease to the steroidal content of oral contraceptives. This study published in the *British Medical Journal* in 1970, took reports of all patients who had thromboembolic disease and used oral contraceptives that had been received by the Drug Safety Committee in the United Kingdom and in Sweden and Denmark. These reports were analyzed for the type of oral contraceptive used, and correlations were calculated between the doses of estrogen and the risk of pulmonary embolus, deep vein thrombosis, cerebral thrombosis and coronary thrombosis or infarction. These data, shown in Table 8, indicate there is a strong correlation between the estrogen content and the incidence of the above disease states within patients in the United Kingdom. In Sweden and Denmark, there was a similar association in venous thrombosis and pulmonary embolism and estrogen content, but no relation to cerebral thrombosis could be found. When the sequential versus combined contraceptives were studied separately, no differences were observed; the relationship held only for estrogen content. In addition, no differences were noted when the two common estrogens, ethinyl estradiol and mestranol, were compared. Chart 8 shows diagrammatically the relationship between estrogen dose and fatal pulmonary embolism, the most dramatic example of the data collected. It is to be noted that these investigators obtained the expected incidence of thromboembolic phenomena by reviewing the percent of market sales attributable to a particular brand of contraceptive. They then multiplied this percent by the total number of patients having the adverse reaction studied (all of whom took oral contraceptives by selection). They gave this example: Ovulen® (ethynodiol diacetate) accounted for 22.23 percent of the total market sales; there were 75 reports of nonfatal pulmonary embolism—75 × 22.23 per 100 = 16.67, which is the number of patients with pulmonary embolism and taking oral contracep-

TABLE 9.—*Comparative Incidence of Superficial and Deep-Vein Thromboembolic Disease in Women of Childbearing Age*†

Based on	*Cases per 1,000 Woman Years*
Normal incidence	
Hospital admissions	0.91 (0.84 - 1.08)
Visits to physicians	2.20 (1.20 - 3.00)
Antenatal incidence	0.61±0.19*
Oral contraceptive studies	0.97±0.62

*Nine month rate extrapolated to 12 months for comparison with other annual rates.

†Reprinted by permission from Drill V: JAMA 219:583, 1972.

tives that would have been expected to have been taking Ovulen. The incidences thus calculated were compared to the actual incidence data.

Similar findings have been reported now in two studies in the United States.[27,28] For example, Sartwell et al[27] performed a retrospective study published in 1969. They identified 175 women, aged 15 to 44, discharged alive from 43 hospitals after an initial attack of idiopathic thrombophlebitis, pulmonary embolism or cerebral thrombosis or embolism. One hundred and seventy-five hospital controls were matched casewise with each case at the hospital according to: residence, time of admittance to hospital, race, age, marital status, parity and pay status. Both groups of patients were free of chronic conditions either associated with thromboembolism or constituting contraindications to pregnancy. Forty percent of the patients who had thromboembolism and 13 percent of the control patients had received oral contraceptives within one month before the time of admittance to hospital. From this study, the relative risk of thromboembolism for the oral contraceptive users was estimated to be 4.4 times that of the non-users. These investigators found the risk was higher with the sequential contraceptives than with combined contraceptives. However, the estrogen content of the two medications was not given nor discussed.

In 1971, Böttiger and Westerholm[29] in Sweden analyzed 400 cases of thromboembolic disease in women receiving oral contraceptives, reported to the Swedish Adverse Drug Reaction Committee. From knowledge of the population use of oral contraceptives in Sweden, they estimated that the risk of having thromboembolic manifestations was 1 in 3,600 users of oral contraceptives, as compared with 1 in 23,000 non-users of oral contraceptives, or 1 in 340 during normal pregnancy. The mortality risks were estimated at 0.9 patients per 100,000 users per year. The patients studied by Böttiger and Westerholm included patients with deep vein thrombosis, cerebral thrombosis, myocardial infarction, both those who survived and those who died of their disease.

In contrast to these series of publications (utilizing selected controls and retrospective studies) which suggest increased incidence of thromboembolic disease with oral contraceptives, three papers have appeared in the *Journal of the American Medical Association,* written by Drill and Calhoun,[30-32] which review the total world literature on this subject and conclude that there is not an increased incidence of thromboembolic phenomena in patients receiving oral contraceptives. The overall incidence of thrombophlebitis in nonpregnant women of childbearing age was obtained from a series of publications which obtained data between 1957 and 1966. Based upon these publications, the incidence of hospital admissions for superficial and deep vein thromboembolic episodes was estimated to average 0.9 cases per 1,000 women per year. If patients who visited the physician in his office were included, the rate increased to an average of 2.2 cases per 1,000 per year. Drill made independent calculations from the Royal College of General Practitioners Study[33] which indicate a rate of about 1.3 cases per 1,000 women per year. Expecting this control statistic, Drill reviewed the incidence of superficial and deep vein thromboembolic disease in all published large-scale studies with oral contraceptives. These data are reviewed in Table 9 and indicate that an average of 0.91 cases per 1,000 women per year was observed. This is not increased over the control population, but is significantly higher than the antenatal group (which is also exposed to estrogen and progestogen). Drill also reviewed all the reported small-scale prospective studies with oral contraceptives and obtained an overall rate of thromboembolism (fatal and nonfatal) from some 53 publications of 1.22 per 1,000 women per year, also not significantly different from controls. Drill went further and took data from Vessey and Doll[25] concerning the incidence of recurrence in women continuing oral contraceptives after having had one thromboembolic episode. Two series of patients were reviewed, one composed of 21 patients and a second of 29 (the 21 original plus eight more) with a history of thrombophlebitis, some of whom had continued taking oral contraceptives. Table 10 presents Drill's summary of Vessey and Doll's data, which revealed no significant differ-

TABLE 10.—*Recurrence of Thromboembolism in Treated and Untreated Women**

	Number Cases	Disease Recurrence: Not Using Oral Contraceptives	Disease Recurrence: Using Oral Contraceptives
1968	21	12 (57%)	9 (43%)
1969	29	17 (59%)	12 (41%)

*Reprinted by permission from Drill V: JAMA 219:583, 1972.

ence between patients who were taking oral contraceptives and those who were not. Drill went on to divide the published studies into prospective studies in which the drug is administered to groups of women and the occurrence of cases of thromboembolic diseases recorded; and retrospective studies, which are analyses of hospital records with selected control groups. He reviewed the 15 large prospective studies and the 53 small-scale prospective studies, and came to the conclusion previously given: "There is no increase in thromboembolic phenomena in women taking oral contraceptives." It is to be noted, however, that these prospective studies did not include selected control groups matched for age, parity, and other such factors, but took the incidence of thromboembolism in the population as a whole as its control. The retrospective studies that we reviewed above are the ones that have indicated increased thromboembolic phenomena. Their controls were selected in the fashion described, although Drill quotes a statistical text of Mainland *(Elementary Medical Statistics)* to correctly point out that retrospective studies cannot be used to prove cause and effect relationship; they can be used to suggest an hypothesis of cause and effect. Prospective studies should be used to prove the relationship. Drill, however, neglects to add that even prospective studies must be designed correctly to include control groups handled in the same fashion as treated groups. The latter has not been true for the prospective studies reviewed by Drill (or existing in the literature for our review). Thus the proof that no cause and effect relationship exists between estrogen containing oral contraceptives and thromboembolic phenomena is on as shaky grounds as is the statement that there is such a relationship.

Goldzieher[34] has critically analyzed some of the publications on thromboembolic hazards that appeared in 1970. He indicates that the incidence of any idiopathic thromboembolic disease has increased strikingly in some countries independent of the introduction of oral contraceptives—in

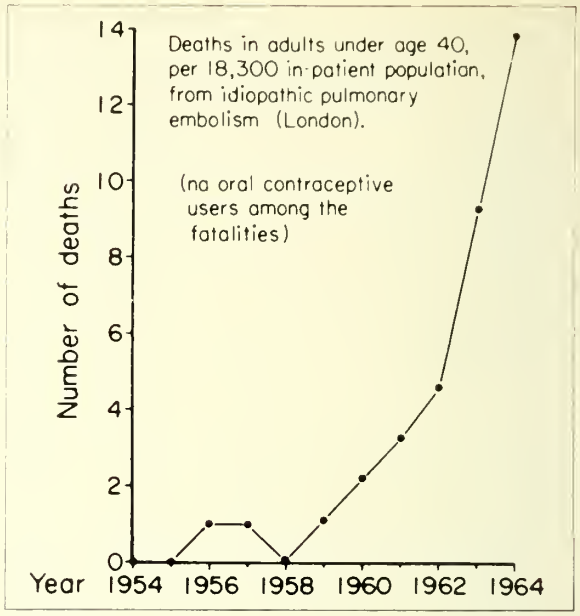

Chart 9.—The change in number of deaths from idiopathic pulmonary embolism in London during the years 1954 to 1964. (Reproduced by permission from Goldzieher JW: Contraception 1:409, 1970)

other words, in patients not receiving oral contraceptives. This incidence is shown on a graph from his publication in Chart 9. This increase of thromboembolic disease may be related to decreased ambulation that has come with increased use of the automobile and other transportation devices, for thromboembolic phenomenon remains very low in certain countries of the world where ambulations remain high. The increase occurs in both sexes and, as indicated in Chart 9, in women who never used oral contraceptives. Goldzieher also points out (as Drill did) the antenatal incidence of thromboembolic disease is not increased over the normal population. Goldzieher summarized data that he collected in a single, closely coordinated, computerized clinical trial of 23,217 women observed monthly for a total of 363,469 cycles. The dropout rate was unusually low in this cycle and the incidence of thrombophlebitis in women examined every month turned out to be surprisingly low—0.56 per 1,000 women per year, very close to the figure previously stated from the general population review of world literature by Drill and Calhoun. Goldzieher criticizes the retrospective studies, previously described, of the College of General Practitioners, stating that the number of thromboembolic patients was small and that patients with predisposing conditions other than pregnancy or postpartum state were not excluded

or commented on. He comments that the possibility of thrombophelebitis being associated with oral contraceptives is masked by the inclusion of such patients. However, a difference was observed even in these diluted sample studies, and Goldzieher states that one must conclude that either the contraceptive-caused thromboembolism is very common (an inference negated by subsequent British studies) or that the comparison is severely biased. The same group of British investigators, Goldzieher points out, have reported an association of meclozine with fetal abnormalities, a finding subsequently shown to be incorrect.

Finally, Goldzieher assembled the mortality risk for women due to pregnancy and various forms of contraceptives. Since the risk of pregnancy per se is greater with other contraceptive devices and lowest with oral contraceptives, the mortality risk from the sum of pregnancy and other contraceptive devices is greater than the sum for oral contraceptives. These data are presented in Table 11.

Certain other studies involving treatment with estrogens, men for atherosclerotic heart disease or prostatic cancer and women for lactation, also bear on our discussion. Daniel el al[35] reported that there was a tenfold increase in thromboembolism in women postpartum receiving 30 to 60 mg of stilbestrol daily as compared with lactating women not receiving the stilbestrol. All eight cases of pulmonary embolism observed occurred in the treated group. In 1963, Stamler et al[36] reported a well controlled study of estrogen therapy for myocardial infarction in middle-aged men. High doses (10 mg conjugated equine estrogens per day) were given to one group of men for three months after a myocardial infarction. The treatment group had a 21.7 percent recurrence; the placebo group had a 4.6 percent recurrence. Two well controlled studies of estrogen treatment of prostatic cancer in men were performed by the cooperative Veterans Administration Hospital group in the United States[37,38a] and one by Bailar reported in *Lancet*.[38b] In the study by Bailar, 5 mg of stilbestrol was given daily and the patients compared with a control group not receiving estrogen. There were increases in deaths due to heart disease and cerebrovascular accidents in the group receiving this high dose of stilbestrol. These data are summarized in Table 12. In the well controlled Veterans Administration Hospital studies, there was also a striking increase in deaths in the men receiving 10 to 15 mg of stilbestrol daily.[37] The study was discontinued when the differences became statistically significant. Later a well controlled study using 5 mg of stilbestrol was carried out.[38a] In this study, in contrast to the report of Bailar[38b] in men post-infarction, 5 mg of stilbestrol did not appear to increase mortality from thromboembolic phenomena. It is to be emphasized that this type of prospective, well controlled study has not been performed in women receiving oral contraceptives.

Cerebrovascular Disease and Oral Contraceptives

We commented earlier on Inman and Vessey's[24] report of the association of cerebral thrombosis and embolism with oral contraceptive use. In

TABLE 12.—*Prostatic Cancer Patients Treated with 5 mg Stilbestrol Daily**

	Estrogen	*No Estrogen*
Total number patients	1,099	1,101
Deaths due to:		
Heart disease	146	103
Cerebrovascular accident	42	26
Pulmonary embolus	16	12

*Reprinted by permission from Bailar JC: Lancet 2:560, 1967.

TABLE 11.—*Death Rates per Million Women per Year Associated with Pregnancy, Contraceptives, and Certain Other Causes*§

	Pregnancies		*Deaths Cause*	
Agent	*Number*	*Total*	*Pregnancy Itself*	*Contraceptive*
No contraceptive	800,000	200-1,000*	200-1,000	..
Rhythm method	230,000	60-300	60-300	None
Diaphragm	200,000	56-280	56-280	None
Condom	100,000	28-130	28-140	None
Intrauterine device	25,000	26-50	6-30	20†
Oral contraceptive	10,000	15-40	3-15	12-24‡

*Range of values from high to low socioeconomic status.
†FDA Advisory Committee on IUCD's, 1968, p. 7.
‡Based on USA and British estimates of risk, respectively.
§Reprinted by permission from Goldzieher JW: Contraception 1:409, 1970

1970, Masi and Dugdale[44] reviewed the English literature on this subject. Several individual or small numbers of case reports of cerebrovascular disease occurring in women taking oral contraceptives appeared in various American and British journals between 1962 and 1968. Walsh et al[45] reviewed the cases of 68 patients with neurological disease. Of these 68, four young patients on long treatment had pseudotumor cerebri, 17 had stroke, 20 had ocular involvement (optic neuritis or retinal vascular disease) and ten had migraine headaches. Obviously, this was not a controlled study but a review of neurologic disease in women receiving oral contraceptives. Other papers appeared, but again, controlled studies did not exist (for examples see Refs. 46-49). Finally, the study of Inman and Vessey[24] and Vessey and Doll[25] appeared which indicated an increased risk of cerebrovascular disease in women taking oral contraceptives. All cases of cerebral thrombosis were reviewed by a neurologist (without knowledge of the oral contraceptive use) and 19 were selected as meeting diagnostic criteria. Eleven (58 percent) had been taking oral contraceptives, whereas 18 percent would have been expected to have been taking them.

The study of Sartwell et al[27] also contained data on 13 patients with idiopathic intracranial vascular occlusion. Eight (62 percent) of the patients took oral contraceptives within one month of their illness; only 1 (8 percent) of the controls had done so. Most recently a collaborative study of stroke in young women was published.[50] For this study 12 neurologists reviewed cases of young women admitted to 91 participating hospitals in a two-year period. Five hundred ninety-eight nonpregnant women, aged 15 to 44 years, who had cerebrovascular disease, were reviewed. A detailed history of contraceptive use was obtained from 70 percent of the patients, and controls were obtained. The control group was selected from women with similar age, race and neighborhood of habitat. The findings which are summarized in Table 13 indicate a considerably greater use of oral contraceptives in the cerebrovascular patient group. The relative risk of cerebral vascular ischemia or thrombosis was estimated to be ninefold greater in women taking oral contraceptives than in those who do not.

In summary, data from well controlled studies of men receiving estrogens in high doses indicate that thromboembolic disease is increased. Similar well controlled studes have not been performed in women. Retrospective analysis of women having thromboembolic disease indicates that the percent taking oral contraceptives is greater than in a selected control group. In contrast, analysis of all the world literature, with summary of the incidence in all publications, fails to reveal an increased incidence of thromboembolism in women receiving oral contraceptives. Women antepartum, in whom high concentrations of estrogens and progestogens exist, do not appear to have increased likelihood of thromboembolic phenomena.

TABLE 14.—*Estimated Death Rate* from Several Causes in Women†*

	Age in Years	
	20-34	35-44
Pulmonary and central thrombo-embolism		
Nonusers of oral contraceptive	0.2	0.5
Users of oral contraceptive	1.5	3.9
Accidents	4.9	3.9
Cancer	13.7	70.1
Complications of pregnancy, delivery and puerperium	22.8	57.6

*Per 100,000 women per year.
†Modified from Inman and Vessey: Br Med J 2:193, 1968.

TABLE 13.—*Non-Matched Comparison of Use of Oral Contraception by Patients and Controls, According to Age†*

	Cases of Stroke			*Hospital Controls*			*Neighbor Controls*		
		Users			*Users*			*Users*	
*Age Years**	*Total Number*	*Number*	*Percent*	*Total Number*	*Number*	*Percent*	*Total Number*	*Number*	*Percent*
15-24	44	22	50.0	34	9	26.5	44	13	29.6
25-34	103	43	41.8	77	16	20.8	109	24	22.0
35-44	282	58	20.6	282	28	9.9	297	31	10.4
TOTALS	429	123	28.7	393	53	13.5	450	68	15.1

*Oral contraceptives used at reference date.
†Reprinted by permission from Collaborative Group Study of Stroke in Young Women. N Engl J Med 288: 871, 1973

It appears likely, based upon all these data, that very high doses of estrogens may increase the risk, but that lower doses may not. Since currently low-dose estrogen-progestogen combined contraceptives are commonly used, any risk that might exist with the high dose may be nonexistent or minimal with the low doses. Table 14 gives some relative incidence of mortality for oral contraceptives taking Inman and Vessey's data as a high estimate example, and comparing this with postpartum state, auto accidents and cancer to help put the figures in perspective. Progestogen-only oral contraceptives have not been implicated with increased risk of vascular disease.[39-43] Although the case for cause and effect of thromboembolic phenomena is on shaky ground, it would appear unwise to use estrogen containing oral contraceptives in women with clear-cut predisposing factors for thromboembolism. Such factors would include congestive heart failure, significant edema from any cause, obesity, varicose veins, and history of thrombophlebitis or embolism. The history and controversy of the relation of oral contraceptives to thromboembolism is an excellent example to point out the great need for carefully controlled clinical experimentation.

Effects of Oral Contraceptives on Carbohydrate Metabolism

GEORGE A. BRAY, MD*

THE INITIAL OBSERVATION of an impaired glucose tolerance in patients receiving oral contraceptives was made over ten years ago.[51] Since that time, this phenomenon has been examined in detail by many observers and has been reviewed several times,[52-54] most recently by Beck.[55] In the following discussion, we will examine this phenomenon in detail and attempt to answer three questions:

1. What are the impairments in glucose tolerance associated with ingestion of oral contraceptives?

2. Is the impairment of glucose tolerance the result of the estrogen, the progestogen or their combination?

3. By what mechanisms does this phenomenon occur?

The impairment of glucose tolerance is illustrated in Chart 10.[56] Two facts emerge: (1) The levels of fasting glucose are not significantly dif-

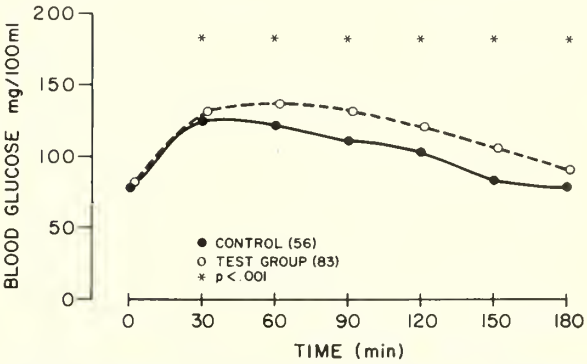

Chart 10.—Effect of oral contraceptives on glucose tolerance. This study adapted from Wynn and Doar[56] shows the impairment in glucose tolerance at all time intervals after the initial administration of glucose. Fasting levels of glucose, however, were normal. (Reproduced by permission from Wynn and Doar: Lancet 2: 715, 1966)

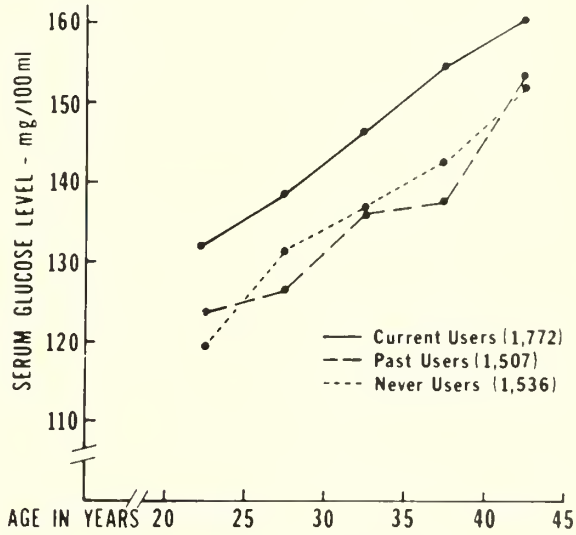

Chart 11.—Effect of age and oral contraceptives on glucose tolerance. The mean one-hour serum glucose concentrations after oral glucose, in current users, past users and non users of contraceptives steroids, is plotted against age. There was an increase in the levels of one-hour glucose value as a function of age. Women taking oral contraceptives had one-hour glucose values approximately 10 mg per 100 ml higher than the women who were not taking contraceptives or women who had previously taken them but had discontinued their use. (Reproduced by permission from Beck et al: Metabolism 22:846, 1973)

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ferent during treatment with oral contraceptives, and (2) glucose concentrations are elevated at all times after oral glucose. Since these early studies, it has become clear that the changes in glucose tolerance are in part related to the specific glucose tolerance. Fasting blood sugar may be normal[56-64] or elevated.[65,66] Whether or not the fasting glucose changes, however, there is a deterioration in oral glucose tolerance with most oral contraceptives and in most studies. The reported number of women whose glucose tolerance worsens, however, varies from one study to another. Of more importance is the fact that the impairment in glucose tolerance is reversible when the oral contraceptives are discontinued (Chart 11).[67] In this chart, the height of the one-hour glucose level after an oral glucose load is plotted as a function of age for women who are taking contraceptives, for women who have never taken contraceptives, and for a group of women who have discontinued taking them. This chart shows three things: (1) That there is an increase in the height of the one-hour glucose value in relation to age—that is, older women, whether on medication or not, have a higher level of glucose one hour after the oral administration of a glucose load than do younger women, (2) that after discontinuing the use of oral contraceptives, the one-hour glucose values return to normal, and (3) that the increase in glucose in women taking oral contraceptives is about 10 mg per 100 ml higher than in the other groups at all ages.

Elevated concentrations of insulin are commonly found in women taking oral contraceptives. This occurs in both the fasted state and during the oral glucose tolerance test. The higher fasting levels of glucose are thought to maintain fasting glucose at normal levels in most women. In addition to the consistent rise in insulin during therapy with oral contraceptives, there is a frequent,[60,61,66,68] although not uniform[62,64] increase in fasting growth hormone. In summary, then, oral contraceptives have a variable effect on fasting glucose which is frequently maintained within normal limits by the elevated fasting levels of insulin. During oral glucose tolerance tests, the rise in glucose and insulin are higher in women taking oral contraceptives than in controls. Fasting growth hormone levels may also be elevated.

Most oral contraceptives contain a combination of an estrogen and a progestational agent. Hence, the impairment in glucose tolerance could result from either agent alone or from their combination. To examine the role of the estrogenic component, Spellacy et al[69] performed intravenous glucose tolerance tests on a group of women before and six months after taking ethinyl estradiol, mestranol or Premarin® (conjugated estrogens, USP). Table 15 shows data for the sum of the glucose levels at 0, 1, 2 and 3 hours on women before and after six months of this treatment. No significant impairment in oral glucose tolerance was brought about by treatment with any of these estrogens for six months. These

TABLE 15—*Effect of Estrogenic Steroids on Glucose Tolerance**†

Drug	*Number*	*Dose mg*	*Total Blood Glucose mg/100 ml*	
			Before	*After 6 Months*
Premarin®	42	1.25	411.9±14.6	431.1±15.6
Mestranol	60	0.08	445.1±17.0	429.3±15.7
Ethinyl estradiol	45	0.05	403.7±13.7	415.7±12.8

*Total glucose is the sum of the glucose values at 0, 1, 2 and 3 hours after an oral glucose load.
†Reprinted by permission from Spellacy: Am J Obstet Gynecol 114:378, 1972.

TABLE 16.—*Effect of Oral Contraceptives on Glucose Disappearance**

	Number Patients	*Duration (year)*	*K*†		*P*§
			Before	*During*	
Norethynodrel 5 mg + mestranol 0.075 mg	31	0.5	1.88±0.38‡	1.46±0.42	<.01
Megestrol acetate 5 mg + 27 mestranol 0.10 mg	27	1	2.05±0.60	1.94±0.55	NS¶
Megestrol acetate 4 mg + ethinyl estradiol 0.05 mg	15	1	2.62±0.32	2.52±0.31	NS
Chlormadinone acetate 0.5 mg	15	1	2.04±0.11	1.80±0.14	NS

*Adapted from Beck et al: Metabolism 22:846, 1973.
†K = the rate of fall of blood sugar in percent per minute.
‡Mean ± SEM.
§P = level of statistical significance.
¶NS = not significant.

data suggest that the estrogenic components of oral contraceptives are not alone responsible for the deterioration in glucose tolerance. One could also conclude from the data that the worsening of glucose metabolism was due to the progestational agent either alone or in combination with the estrogen. A similar conclusion is reached by comparison of the results of three studies with two estrogenic and two progestational compounds (Table 16).[57,64,70] The data in this table show a significant impairment in intravenous glucose tolerance when mestranol and norethynodrel were given as compared to mestranol or ethinylestradiol combined with megestrol, a different progestational agent. The importance of the progestational agent is also suggested in other studies. With progesterone alone,[70] there was no impairment in intravenous glucose tolerance. Of five patients who received norethindrone and mestranol, all had abnormal glucose tolerance test results.[71] When ethynodiol diacetate was the progestational agent, between 12 and 30 percent of the patients showed abnormalities in glucose tolerance.[63,65,72] Norethynodrel was also associated with impaired glucose tolerance.[73,74] Both of these progestational agents are derivatives of 19-nortestosterone. When chlormadinone acetate, a derivative of 17-αhydroxyprogesterone, was employed as the progestational agent, the percent of abnormal curve declined (Table 16).[75,76] These data, then, strongly suggest that it is the progestational agent which is principally involved in the impairment of glucose tolerance. In summary, it would appear that the impaired glucose tolerance and elevated level of insulin are primarily due to the progestational agent employed. The estrogenic component, however, may well have a synergistic effect. Oral contraceptives containing derivatives of nortestosterone appear to impair glucose tolerance more than those which are derivatives of progesterone.

The mechanism for these effects of oral contraceptives on glucose tolerance is unclear. One hypothesis has suggested that increased secretion of growth hormone may lead to the impaired glucose tolerance.[60,61,66,68] The possibility that growth hormone is involved was tested recently.[68] Normal and hypopituitary women were given an oral contraceptive containing mestranol and norethindrone. Tolbutamide was used to test the patients before and while receiving contraceptives. The anti-fertility drug blunted the fall in glucose and free fatty acids and enhanced the rise in growth hormone in the normal women. In the hypopituitary patients, oral contraceptives did not modify the response to tolbutamide. These differences resulting from the presence or absence of endogenous growth hormone lend support to the concept that growth hormone may be responsible for the impaired glucose tolerance. The studies of Spellacy et al[69] with estrogenic agents, however, do not support this concept. Both mestranol and ethinyl estradiol raise fasting growth hormone but are not associated with a deterioration in glucose tolerance. Thus, the mechanism for the impaired glucose tolerance seen with oral contraceptives still remains unclear.

Contraceptives and Lipid Metabolism

ROBERT H. FISER, MD*

DISORDERED LIPID METABOLISM is a troublesome and potentially serious side effect of contraceptive steroid therapy.[77-79] Although all lipid classes are affected by contraceptive use, elevations in plasma triglyceride and cholesterol concentrations have been the most consistent findings.[77-80] Increased levels of triglyceride and cholesterol have been used to explain the increased atherogenic index and the increased[81] incidence of myocardial infarction[82] and cerebral vascular accidents[83] in women using the pill compared with premenopausal women not using these steroids. Although there is no definite evidence on the causal relationship of disordered lipid metabolism to vascular disease with use of these drugs,[84] even this possibility makes it of clinical importance. Elevated triglyceride levels take on added significance with the recent report of Carlson and Böttiger 1972,[85] who found hypertriglyceridemia to be as great a risk factor for ischemic heart disease as hypercholesterolemia.

Increases in triglycerides and cholesterol concentrations are progressive, begin within a few weeks after beginning contraceptive therapy,[84] are dose-related[78,81,84] and plateau after several months. The elevated levels often persist after dis-

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TABLE 17.—*Lipid Response to Contraceptive Steroids*

Frequency of Lipid Response	*Pretreatment Lipoprotein Pattern*	*Lipid and Clinical Response*
Usual	Normal	Slight increase in triglycerides and cholesterol
Unusual	Type I, IV, V	1. Moderate increase in triglyceride and cholesterol 2. Occasional massive increase in triglycerides and pancreatitis

continuance of the pills[84] but usually return to previous levels within six months.[77] The increase in triglyceride concentrations in patients receiving contraceptives medications have been associated with concomitant increases in plasma levels of very low density (VLDL), or prebeta; low density, (LDL), or beta and/or high density (HDL) alpha-lipoproteins.[81,86-88] One report described a significant decrease in cholesterol esters.[87] Although few data are available concerning the other major lipid classes, phospholipids have been reported to be significantly elevated with associated increases in VLDL and HDL lipoproteins.[88,89] Variable responses have been reported in free fatty acids—increased in one study[87] and unchanged in another.[86]

Plasma triglyceride levels are significantly increased in women using contraceptives, but the increase is slight and rarely exceeds the upper limits of normal of 150 mg per 100 ml[90] (Table 17). However, in patients with underlying hyperlipoproteinemic states (Type I, IV and V)[91] pronounced hypertriglyceridemia often associated with acute pancreatitis can occur.[92-95] Moreover, the most common lipoprotein abnormality consists of elevated cholesterol and triglycerides, with the chylomicron test (serum or plasma refrigerated overnight) showing slight turbidity and cloudiness after standing, which suggests that triglycerides in this disorder are primarily of endogenous origin. In patients with underlying lipoprotein abnormality of this type (Type IV), striking elevations of serum triglyceride levels may develop while taking the continued estrogen-progestogen contraceptive agents.

Types I and V are uncommon types of hyperlipoproteinemia but patients with these underlying disorders are affected adversely by contraceptive therapy. In these disorders, cholesterol and triglycerides are slightly to decidedly elevated. On standing, the plasma shows both a cream layer on top over a turbid infranate in Type V and clear infranate in Type I, showing that both endogenous as well as exogenous triglycerides are increased. One could also be aware of other disease states and associated illnesses that can cause secondary abnormalities of lipid values (Table 18).[96]

TABLE 18.—*Secondary Type IV Hyperlipoproteinemia**

Endocrine and metabolic
- Diabetes mellitus—
  - Juvenile
  - Maturity onset
- Hypothyroidism
- Hypopituitarism
- Gout
- Lipodystrophy
- Pregnancy

Renal
- Nephrotic Syndrome
- Uremia
- Renal Transplantation
- Hemolytic-Uremic Syndrome

Acute and transient
- Post myocardial infarction
- Pancreatitis
- Burns

Storage Diseases
- Lecithin—cholesterol acyl transferase deficiency
- Nieman Pick
- Gaucher
- Liver glycogen disease
- Malignancies
- Paraproteinemia
- Hepatoma
- Others
  - Progeria
  - Werner's Syndrome

"Exogenous" causes
- Contraceptives
- Alcohol
- Estrogens in males
- Steroid therapy

*Adapted from Kwiterovich PO Jr, Margolis E: Type IV Hyperlipoproteinemia. Clinics in Endocrinology & Metabolism 2:41-71, 1973.

The estrogen component of oral contraceptives is responsible for the lipid alterations but in view of the complex synthesis, secretion, and catabolism of triglycerides there are many possibilities for a biochemical defect. The defect responsible for these alterations in patients using oral contraceptives as well as patients with the basic defect of Type IV hyperlipoproteinemia, has not been defined.[96] In its most simple form in the postabsorptive state, the plasma triglyceride level is determined by balance between the influx of VLDL triglycerides from the liver and the efflux of VLDL

triglycerides from the bloodstream. Hypertriglyceridemia could thus result from (1) an increased rate of VLDL synthesis, (2) a decreased rate of triglyceride removal or (3) some combination of these two.

An increased rate of synthesis could result from increased peripheral resistance to insulin action, as has been outlined previously.[97] (See previous discussion.) Hormonal modulation or changes in insulin:glucagon ratios also may be important. Reaven et al[97] concluded that in Type IV hyperlipoproteinemic states the high insulin levels, along with increased impedance to glucose uptake, resulted in increased synthesis and release of triglycerides from the liver. Increased free fatty acids can also contribute to increased production, for high circulating levels of free fatty acids are known to stimulate very low density lipoprotein synthesis in the liver. Kekki and Nikkila[84] suggested that oral contraceptives in premenopausal women not only increase triglyceride production rate by the liver but also increase the efficiency of removal. Therefore, the maximal turnover rate was apparently unaffected. These data suggested that the increase in plasma triglyceride concentrations observed in women using contraceptive steroids are due to acceleration of triglyceride effux. Moreover, these effects on triglyceride metabolism are produced by one cycle of treatment and no reversal of these effects was observed one month after discontinuation of the drug. In these studies[84] the triglyceride concentration and production rate was significantly correlated to the degree of intake of contraceptive preparations while the removal efficiency was not.

Earlier data had suggested that oral contraceptives might alter lipid metabolism primarily by impairing removal of effux, presumably by a decrease in post heparin lipoprotein lipase activity.[86,98] In contrast, neither oral[98] nor intravenous fat tolerance[86] was shown to be impaired in oral contraceptive users. Hazzard et al[99] suggested that there are normal levels of lipoprotein lipase present in these patients but an acquired resistance to heparin accounts for the impaired post heparin lipolytic activity. It is likely that for full interpretation of the mechanisms producing hyperlipidemia, dynamic studies utilizing radioisotopic techniques will be necessary, with simultaneous correlation of the hormonal changes on fat and carbohydrate metabolism both at the hepatic and cellular level.

The importance of hormonal control comes from several recent reports that suggest insulin plays a key role in hyperlipidemic states; and the high insulin levels associated with the use of these agents may be the primary defect. High carbohydrate diets are associated with a positive correlation between a rise in serum insulin and triglycerides.[100,101] Insulin also affects synthesis and removal of serum lipoproteins. Glucose loading stimulates hepatic triglyceride secretion in man,[102] and in rat.[103a] Insulin may also have more specific effects on lipoprotein synthesis. In addition insulin may increase triglyceride production by stimulating hepatic fatty acid synthesis or exert effects rapidly by altering concentration of metabolic intermediates in the liver.[96] The antilipolytic effect of insulin on adipose tissue lowers serum free fatty acid levels thus reducing flow of free fatty regulating production.[103b] Insulin also is required for normal synthesis of lipoprotein lipase[103c] affecting removal of triglycerides from circulation.

Progestational steroids are known to lower serum triglyceride levels and have been reported to bring about amelioration of lipid abnormalities in women with familial Type V hyperlipidemia.[104] Thus the combined contraceptives pills contain two agents with opposing effects on serum triglycerides. Perhaps the effect of the progestational components of these drugs is that severe hypertriglyceridemia is not more common. This effect may protect most of the estrogen-sensitive women who would otherwise come to have pronounced hyperlipoproteinemia when treated with oral contraceptive agents. Progesterones presumably work by stimulating lipoprotein lipase activity and thus enhancing removal of triglycerides.[104]

It is possible that the mild elevations in serum lipid have no serious sequelae, but the question can be answered only by prospective long-term studies. However, in patients with Type I, IV and V hyperlipoproteinemic states, birth control pills can precipitate severe and prominent abdominal symptoms and pancreatitis.[92,93,105] Therefore, previous knowledge of patients with these hyperlipidemic states is helpful in the differential diagnosis of acute abdominal pain and can prevent unnecessary laparotomy.

These experiences suggest caution in the use of oral contraceptives in patients who already have elevated lipids, and should alert all physicians to the possibility of pancreatitis secondary to hyperlipidemia in the patients receiving oral contraceptive agents. It seems apparent that a fasting serum triglyceride and cholesterol levels should be de-

termined and chylomicron tests should be obtained before prescription of oral contraceptives. If abnormalities are found, other types of birth control devices should be evaluated, considering in each case the risk of pregnancy versus the risk of severe hyperlipidemia. If contraceptive steroids are utilized, only the smallest dose of estrogens should be used and close follow-up with periodic measurement of plasma lipids is necessary.

Complications of Systemic Contraceptive Agents: Hypertension

ADA R. WOLFSEN, MD*

INCREASED BLOOD PRESSURE associated with oral contraceptive therapy was first reported by Owen in 1966.[106] Laragh et al in 1967[107] reported a temporal relationship between the initiation of oral contraceptive therapy and the onset of systolic and diastolic hypertension in six of eleven patients. He also observed improvement or correction of hypertension after withdrawal of the medication.

Prospective studies by Tyson,[108] Saruta[109] and Clezy[110] indicated a 15.5 percent, 18 percent and 4.05 percent incidence, respectively, of sustained systolic and diastolic hypertension with oral contraceptive therapy. The lower incidence of hypertension in Clezy's study was attributed to different diagnostic criteria and difference in the population studies. Women who remained normotensive during therapy also had a small significant increase in systolic blood pressure.

Spellacy and Birk reported a similar occurrence of hypertension ranging from 5 percent to 7 percent in oral contraceptive users, in those taking ethinyl estradiol and in those taking mestranol, whereas hypertension was not found in women using intrauterine devices, progestogens or conjugated estrogens.[111] This study showed the estrogen component of combined oral contraceptives was the important agent for the development of hypertension.

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RENIN CONCENTRATION

RENIN SUBSTRATE —RENIN→ Angiotensin (Renin Activity)

RENIN SUBSTRATE:	Amount angiotensin generated by additional excess renin
RENIN ACTIVITY	Amount angiotensin generated by entire system, without additions
RENIN CONCENTRATION	Amount angiotensin generated in presence of fixed amount of renin substrate

Chart 12.—Components of the renin-angiotensin system. (Reproduced by permission from Saruta T, et al: Arch Intern Med 126:621, 1971, "Copyright 1970, American Medical Association")

During estrogen therapy an increase in renin substrate, resulting in activation of the renin-angiotensin system, has been observed. It is currently believed that renin, secreted by the juxtaglomerular cells, cleaves circulating renin substrate, an alpha 2 globulin synthesized in the liver to form the decapeptide angiotensin I which is rapidly cleaved predominantly in the lung, producing angiotensin II. The actions of angiotensin II include contraction of smooth muscle, stimulation of aldosterone secretion and suppression of renin release by the kidney. Angiotensin II is rapidly metabolized in the vascular bed, having a half life of about 1 minute.[112]

Chart 12 summarizes the methods of measurement of the various components of the renin-angiotensin system. Renin substrate is the amount of angiotensin generated by additional excess renin. Renin activity is the amount of angiotensin generated by the entire system without additions. This reflects endogenous renin substrate and the amount of renin circulating. Renin concentration is the amount of angiotensin generated in the presence of a fixed amount of renin substrate.

The changes in the components of the renin-angiotensin system in 13 women who remained normotensive on combined oral contraceptive therapy were reported by Cain et al.[113] There were pronounced elevations of angiotensin II observed within five days of the beginning of therapy. There were less pronounced increases in plasma renin substrate and renin activity. Plasma renin concentration was suppressed during oral contraceptive therapy; this was attributed to the inhibition of renin secretion by increased levels of angiotensin II. All values returned to the normal range one month after withdrawal of treatment, and fell below the normal mean one month later.

Similar changes in the renin-angiotensin system have been observed by Helmer and Griffith in

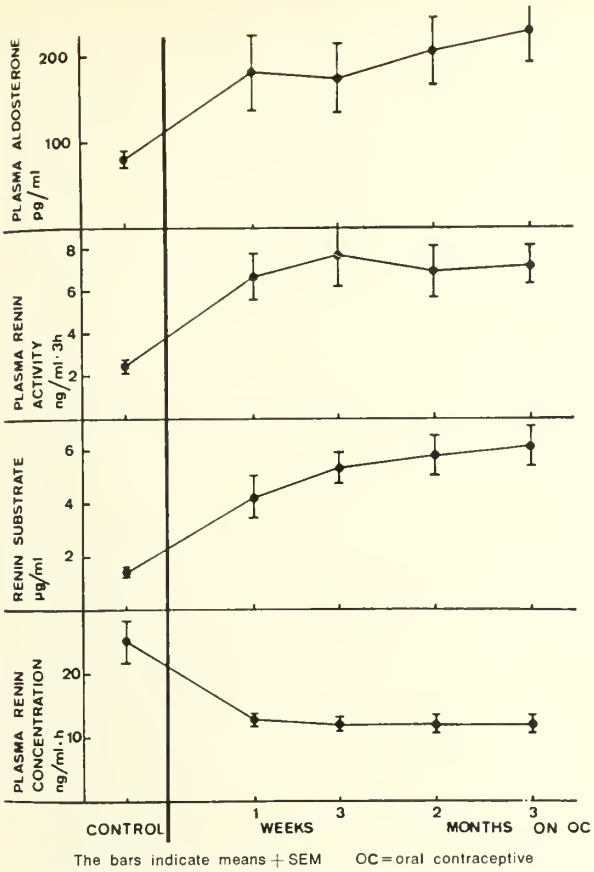

Chart 13.—Changes in plasma aldosterone, plasma renin activity, plasma renin substrate, and plasma renin concentration during the first 3 months of contraceptive therapy. (Reproduced by permission from Beckerhoff R, et al: Lancet 1:1218, 1973)

estrogen-treated rats; estrogen treatment caused a rapid increase in plasma renin substrate.[114] This was followed by increased plasma renin activity and decreased plasma renin concentration. This ability to increase renin substrate appeared to be a common property of all the estrogens tested.

Chart 13 illustrates the changes in plasma aldosterone, renin activity, renin substrate and renin concentration induced by oral contraceptive therapy in ten normal women reported by Beckerhoff.[115] Mean plasma aldosterone before treatment was 83 pg per ml; this rose to 183 pg per ml within one week of therapy, and to 229 pg per ml after three months of therapy. Mean plasma renin activity increased 268 percent, renin substrate increased 339 percent and renin concentration fell 50 percent within one week. These women gained an average of 1 kg in body weight during the time of observation. This was attributed to salt and water retention from increased aldosterone activity. Mean blood pressure was 105/72 mm of mercury before therapy and 106/73 after three months of therapy, indicating that the activation of the renin-angiotensin-aldosterone system was well compensated.

Hemodynamic changes in normotensive women on oral contraceptives were reported by Cain et al.[113] Average cardiac output increased significantly by 1.07 liters per minute; blood volume increased 454 ml and body weight increased 1.14 kg. These changes were associated with a significant increase in mean systolic blood pressure of 3.4 mm of mercury, an increase in mean diastolic pressure of 1.5 mm and a rise in mean blood pressure of 2.4 mm.

It has been suggested that hypertension may result from failure of the negative feedback suppression of renin secretion which normally minimizes the increase in renin activity resulting from increased renin substrate concentration. Saruta,[109] in a prospective study, reported renin substrate and renin concentration levels were higher in women who became hypertensive on oral contraceptives than in those who remained normotensive. However, there was no significant difference in renin activity in the normotensive compared with the hypertensive group. Therefore, there is no evidence for a defective feedback mechanism in the women who become hypertensive with oral contraceptive therapy.

Beckerhoff's study of 11 women in whom hypertension developed while they were taking oral contraceptives suggested that a profound decrease in plasma renin concentration during therapy was associated with reversibility of the hypertensive state when therapy was discontinued, whereas less profound suppression of plasma renin concentration was associated with sustained hypertension after therapy withdrawal.[116]

Since changes in the renin-angiotension-aldosterone system are not significantly different in the women who become hypertensive than in the women who remain normotensive on oral contraceptives, other factors have been postulated as causes of the hypertension. Changes in angiotensin II metabolism or minimal renal disease have been postulated but have not been documented in the women in whom estrogen-induced hypertension develops. There is some evidence of a genetic predisposition to hypertension in the women who become hypertensive with estrogen therapy. Spellacy and Birk found a 38 percent frequency of hypertension in women who had previously had hypertension during pregnancy, compared with a

9 percent frequency in women with a negative history.[111] Clezy reported a 58 percent incidence of hypertension on at least one visit in women with a positive history of hypertension during pregnancy, compared with a 23 percent incidence in women with a negative history.[110] He also observed a 53 percent incidence of hypertension on one or more visits during oral contraceptive therapy in women with a parental history of hypertension compared with a 30 percent incidence in those with a negative family history.

It seems likely that the estrogen-induced changes in the renin-angiotension-aldosterone system act on the background of genetic predisposition for hypertension, to produce significant hypertension in a small percentage of persons.

Liver Disease and Abnormalties of Laboratory Tests

DELBERT A. FISHER, MD*

THE STEROID HORMONES in contraceptive preparations exert a number of metabolic effects on the liver. In addition to the alterations in carbohydrate and lipid metabolism already discussed, these hormones modify the rate of synthesis and secretion of a variety of plasma proteins, particularly those that bind hormones and metal ions. The protein most thoroughly studied is thyroxine binding globulin (TBG), an interalpha globulin which is the primary carrier protein for thyroid hormones in serum. The administration of estrogens to euthyroid subjects results in increased serum concentrations of TBG, with the result that serum thyroxine and triiodothyronine concentrations increase. Free hormone concentrations, however, are unchanged after equilibrium is reestablished and hormone production rates remain unchanged.[117-120] In contrast, androgenic hormones and a number of synthetic progestational agents, including norethandrolone and methandrostenolone, reduce serum TBG and thyroid hormone concentrations, also without altering free thyroxine concentrations or thyroid hormone turnover rates.[120-123] These changes in TBG concentration which occur with estrogen or androgen administration are associated with reciprocal changes in the plasma levels of thyroxine binding prealbumin (TBPA).[123]

During therapy with oral contraceptive agents combining estrogen and a progestational steroid, the effect of estrogen on TBG synthesis predominates; that is, a significant increase in serum TBG concentration occurs.[119,124] However, there is no change or an actual increase in serum TBPA concentration.[124,125] It is presumed that these changes reflect changes in synthesis and secretion of these carrier proteins by the liver, since degradation rates are not altered.[123]

More recently, estrogen has been shown to increase plasma concentrations of corticosteroid binding globulin, testosterone-estradiol binding globulin and ceruloplasmin (copper binding protein),[126-128] and these binding protein levels as well as serum levels of transferrin (iron binding protein) and transcobalamin (vitamin B_{12} binding protein) are increased in women taking contraceptive steroid hormone preparations containing estrogen and a progestational agent.[125,129-134] In this regard, administration of these drugs stimulates the changes in serum protein concentrations observed during pregnancy. The increases in these binding protein concentrations result in increased serum levels of the bound hormones, metals or vitamins, but, by analogy with the normal thyroid hormone turnover rates in patients with increased TBG levels, turnover rates and body economy of the hormones, metals, or vitamins are thought to be unchanged.

Increased concentrations of a second group of plasma proteins also occurs; these act as precursors of more active compounds by serving as substrates for a series of enzyme systems. They include angiotensinogen (or renin substrate), plasminogen and fibrinogen.[125,132] Plasma levels of alpha antitrypsin, $beta_{1c}$ globulin, hemopexin and $alpha_2$ macroglobulin also tend to increase, whereas plasma concentrations of the acute phase reactants, orosmucoid and haptoglobulin, decrease; serum albumin concentrations increase slightly if at all.[125,129,132] These changes in serum protein concentrations are summarized in Table 19.

The levels of beta lipoproteins tend to increase and are discussed more fully in the section dealing with serum lipid alterations. The changes in renin substrate are discussed under hypertension.

All of these effects presumably are due to the

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influence of estrogenic and progestational steroids or of both, on hepatic synthesis and secretion of these several classes of serum proteins. The liver appears to be extremely sensitive to sex hormone action.[135] But whether the effects of androgens and estrogens differ in the case of the individual proteins, as in the case of TBG synthesis, or whether there are additive or potentiating effects of the estrogen and progestogen, is not clear.

The mechanism of the steroid effect(s) also is unclear. It has been shown that there are specific steroid binding proteins in cell cytosol of estrogen and progesterone target tissues which are involved in the transport of the steroid to the nucleus where genome activation and stimulation of ribonucleic acid (RNA) synthesis occur, followed by enhanced protein synthesis.[136] Cytosol receptors for estradiol do not appear to be present in liver, and incubation of rat liver nuclei with estradiol in rat uterine cytosol does not increase the already high levels of RNA polymerase activity.[136] Thus, whether the alterations by steroid hormones of the levels of the several serum proteins presumed to be synthesized by the liver represent a primary or a secondary effect of the hormones remains to be defined.

Both the estrogen and progestational steroid in most oral contraceptive preparations are 17-α-alkyl substituted compounds, and such steroids, as well as methyl testosterone, are known to produce cholestasis and hepatic dysfunction.[122,137] Hepatic excretory function measured by the disappearance of sulfobromophthalein (BSP) from the circulation is reduced in experimental animals by a number of natural and synthetic estrogens;[138] in man, it is excretion rather than conjugation of the dye that seems to be impaired.[139] In addition, large doses of estrogen or androgen will impair BSP excretion in normal humans.[122,137,140,141] Progestational steroids also have been shown to inhibit hepatic glycuronyl transferase activity *in vitro*.[142] And all of these drugs may produce elevations in serum bilirubin, alkaline phosphatase, and transaminase activities.[122,137]

During therapy with oral contraceptive preparations containing estrogen and a progestational agent, increases in serum transaminase concentrations (SGOT and SGPT) occur in 5 to 20 percent of women and increases in BSP retention in 20 to 40 percent. These alterations usually are mild and are not associated with symptoms, and serum bilirubin concentrations usually are normal.[137,143,144] There is evidence to suggest that these manifestations may be more frequent and severe in postmenopausal than in pre-menopausal women; in two small series, all of 16 women manifested BSP retention (ranging from 20 to 40 percent) and elevated serum transaminase levels.[137] It is not clear whether these effects are due to the estrogen or the progestogen; there is some evidence to suggest that both components may be required.[137,145]

Rarely, and there are now some 40 reported cases,[137] malaise, nausea, pruritis, and jaundice have occurred a few weeks after the patient has begun taking oral contraceptive steroid medication. These symptoms are associated with increased serum bilirubin and transaminase levels, and liver biopsy reveals dilation of bile canaliculi. By electron microscopy one can see shortening or disappearance of the microvilli, intracytoplasmic dense bodies (referred to as mitochondria-like organelles), dilation of the smooth endoplasmic reticulum and the appearance of myelin figures within mitochondria.[137,146] Cessation of contraceptive therapy usually leads to complete remission within a few weeks or months. Impaired BSP and bilirubin excretion are commonly observed late in pregnancy[147,148] and in a few instances may be of sufficient degree to produce jaundice. In these women the jaundice usually will recur with each pregnancy.

About one-third of the women in whom jaundice developed with oral contraceptive steroid therapy gave a history of having experienced recurrent jaundice of pregnancy.[137] Recurrent jaundice of pregnancy and the jaundice sometimes seen with contraceptive steroid therapy are very similar. In both instances, systemic manifestations are minimal and biopsy reveals predominantly cholestasis. And in both instances there appears to be a predisposition to jaundice with exposure to increased steroid hormone levels. Why these few women are so predisposed is unclear. In any case, women with a history of acute liver disease in the past or jaundice during pregnancy or those with evidence of acute or chronic liver disease should not be given contraceptive steroid medication. Moreover, all women in whom pruritis or jaundice develops during the first few cycles while taking these drugs should have appropriate testing for hepatic dysfunction. If the serum bilirubin levels are elevated or there is more than mild BSP retention or mild elevation of serum transaminase activities, the drugs should be discontinued.

Zinc metabolism has been studied in patients taking oral contraceptive drugs and serum levels

have been found to be reduced.[149] The reason for this is not clear. Serum zinc levels are reduced in patients with hepatic dysfunction, and in such patients zinc excretion in urine is increased and hepatic zinc concentrations are reduced.[150] It has been suggested that a state of conditioned zinc deficiency exists in patients with liver dysfunction, and it is possible that oral contraceptive steroids, by altering hepatic zinc metabolism, produce a similar rate of zinc deficiency.

Another interesting aspect of the effect of contraceptive steroids on the liver is the tendency for these agents to increase mitochondrial delta-amino-levulinic acid synthetase (DALAS) activity.[151] Increased hepatic DALAS results in greater synthesis of heme protein and porphyrins[151] and increased urinary porphyrin excretion has been observed in women taking oral contraceptive steroid drugs.[151,152] Oral contraceptives also can have an ameliorative effect on acute intermittent porphyria associated with the menstrual cycle or pregnancy.[151] Segal and Atkinson[151] have suggested that the increased heme synthesis may also enhance hepatic synthesis of microsomal cytochrome oxidase P-450, which is localized to smooth endoplasmic reticulum and involved in the metabolism of exogenous chemicals as well as endogenous substrates. But this has not yet been investigated.

Finally, there is a recent report of seven patients ranging in age from 25 to 39 years who presented with benign hepatomas after having taken oral contraceptive drugs for periods ranging from six months to five years.[153] Whether the oral contraceptive drugs played any role in the development of these tumors is unclear. Further study is necessary to clarify this problem.

Complications of Systemic Oral Contraceptive Therapy: Neoplasm—Breast, Uterus, Cervix and Vagina

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ADMINISTRATION OF THE ACTIVE INGREDIENTS of oral contraceptive agents—namely, compounds with estrogen or progesterone-like actions, or ablation of their actions, has been used extensively in the treatment of cancer of the sex hormone target organs. This approach has not been entirely empirical, but is based on studies in animals which suggested that increases in the production of the sex hormones or alterations in their metabolism are important factors in the development of cancer of the sex hormone target organs. In the case of the oral contraceptive agents, these target organs include the breast, uterus, cervix and vagina, and much research has been done in an attempt to define the role of sex steroids in the production, prediction and remission of these cancers. Recently the evidence for and against the hypothesis implicating abnormalities of secretion or metabolism of sex steroids in these cancers has been extensively reviewed and criticized.[154] This present overview is confined to a consideration of the potential carcinogenic effect of oral contraceptive agents in the induction of these cancers, and of the possibility that they may be important in reducing the risk factors for these malignant lesions.

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Breast

There is still considerable disagreement as to the endocrine status of women with carcinoma of the breast. The excretion of urinary estrogen metabolites by these patients has been reported to be high, normal or low.[154,155] It had also been postulated that the ratio of excreted estriol/estrone plus estradiol, might be important in the cause of the disease.[156] In a large demographic study, Asian women, who have a low incidence of mammary cancer, had a higher estriol ratio than American women, who have a much higher incidence of breast cancer.[157] However, more recently other investigators have disputed this conclusion.[155] In a study done by these investigators, total estrogen excretion in premenopausal women whose breast carcinoma was stage I to II was significantly lower than in normal controls. Post-menopausal women with breast carcinoma stage III-IV had a significant elevation of the estrone fraction. Conse-

quently, these investigators concluded that high estrogen excretion per se could not be an etiological factor in human breast carcinoma. In addition, they found a higher proportion of estriol in premenopausal patients with carcinoma of the breast in all stages, suggesting that estriol was not protective or antagonistic to other potential carcinogenic estrogens in humans. That estriol might be protective in preventing the appearance of breast carcinoma had been previously suggested.[158,159] Finally, in men with breast carcinoma, a significant increase of the estriol fraction with a corresponding reduction of the estrone fraction had been reported.[160] Thus, these studies argue against a clear contention that estrogens are a significant contributing factor in the pathogenesis of mammary cancer.

Similarly, studies of *in vitro* breast tissue metabolism are conflicting. Breast cancer tissue *in vitro* demonstrated increased estrogen uptake when compared with normal tissue in one study.[161] However, the uptake of 3_H estradiol by human breast tissue *in vitro* has been found to be very variable, with no correlation between uptake and histological classification of the tumor. Nor was uptake influenced by previous treatment with various androgens.[154] In humans, tumors have not been shown to have specific uptake of progesterone or testosterone, despite the occasional clinical response to testosterone therapy.[154] Nevertheless, *in vitro* studies have recently demonstrated that some breast cancer tissue is testosterone-dependent—that is, it is metabolically more active in the presence of testosterone added to the incubation medium—and that this tumor dependence can be inhibited by anti-androgens including estradiol.[162] When *in vitro* tumor dependence on testosterone was inhibited by estradiol, the clinical response to estrogen therapy was good; where the tumor survived well with estradiol *in vitro,* the clinical response to estrogen therapy was predictably poor. The mechanism for this protective effect of estrogens on some breast carcinomas is not known, but it may relate to estrogens ability to inhibit 5 alpha reductase,[163,164] the enzyme required for the final conversion of testosterone to its active metabolite dihydrotestosterone. The ability of normal or malignant breast tissue to synthesize testosterone and dihydrotestosterone has been recently demonstrated *in vitro.*[165,166]

With regard to the incidence or risk factor for the development of breast carcinoma among users of oral contraceptive agents, the recently published report from the Boston Collaborative Drug Surveillance program showed that breast cancer had not developed in any of 4,700 young women taking oral contraceptive agents for more than five years.[167] Although these patients were relatively young, it does suggest that there is no evidence for a higher risk factor of breast carcinoma in women taking oral contraceptive agents than in non-users. Indeed, there was a negative association between the use of oral contraceptive agents and benign breast tumors, particularly for fibroadenoma. These findings are in accord with results of previously published studies where the incidence of fibrocystic and fibroadenomatous disease of the breast among oral contraceptive agent users was unaltered or diminished when compared with non-users.[168-172] In summary, despite many clinical investigations there is no direct link between oral contraceptive use and the development of breast carcinoma or fibroadenoma, nor are there uncontested alterations in the metabolism of estrogens by patients with mammary cancer or by the cancer itself, such that the estrogenic or progestogenic components of oral contraceptive agents could be implicated in the genesis or exacerbation of mammary cancer.

Carcinoma of the Endometrium and Cervix

There have been attempts to implicate alterations of estrogen secretion or metabolism as etiological factors in carcinoma of the endometrium and cervix. The amount of estrogen excreted in urine by women with cervical cancer has again been variously reported to be decreased, normal, or increased,[173] and minor alterations in estrogen metabolism have been reported and disputed.[174,175] It is fair to summarize that there are no biochemical data showing that high estrogen production is an etiological factor in these diseases. And the metabolism of estrogens is similar in patients with endometrial carcinoma and normal patients. However, there is one study purporting that carcinoma *in situ* of the uterine cervix was increased among users of oral contraceptive agents, but pre-therapy cytologic examinations were not done in this group of patients, and thus the study was not adequately controlled.[176] In contrast, there is evidence that synthetic progestogens depress mitosis in uterine cancer cells.[177] In general, there has been no correlation between human tumors and excretion of progesterone derivatives, although progesterone can act as a synergist or antagonist to certain animal tumors.

TABLE 19.—*Alterations in Serum Protein Concentrations in Women During Therapy with Estrogen-Progestogen Oral Contraceptive Preparations**

Protein	*Change in Concentration During Contraceptive Therapy*
Thyroxine binding globulin	++
Prealbumin	±
Corticosteroid binding globulin	++
Testosterone-estradiol-binding globulin	++
Ceruloplasimin	+++
Transferin	+
Transcobalamin	+
Renin substrate	+++
Plasminogen	++
Fibrinogen	+
$Alpha_1$ antitrypsin	++
$Beta_{1c}$ globulin	+
Hemopexin	+
$Alpha_2$ macroglobulin	+
Albumin	±
$Alpha_1$ acid glycoprotein	−
Orosomucoid	−
Haptoglobin	−

*Modified from Lipsett et al: Ann Intern Med 74:251, 1971.

Carcinoma of the Vagina

One very notable exception to the general exclusion of oral contraceptive agents as etiological factors in carcinoma of the vagina is the recent appreciation of the link between the use of certain synthetic estrogen-containing oral contraceptive agents in early pregnancy and the subsequent development of clear-cell vaginal carcinoma in the teen-aged daughters of the women who used them.

In 1970 Herbst et al reported on seven female patients aged 15 to 22 years with adenocarcinoma of the vagina, who had been seen at one hospital in the period 1966 through 1969.[178] This cancer, also referred to as clear-cell or endometrial type, is rare even in women over the age 50 years, in whom vaginal cancer is usually of the epidermoid type. The presenting symptoms and signs were prolonged vaginal bleeding, mistaken initially for anovulatory bleeding because it occurred in young women. Routine cytologic examination was negative, and the tumors were not palpable by rectal examination. Hence there was delay in correct diagnosis, which was made only at direct vaginal examination. Histologically the majority of tumors consisted of tubules and glands lined by clear cells containing glycogen. There was also a high prevalence of vaginal adenosis in these patients.

In a carefully controlled epidemiological investigation, Herbst et al discovered that seven of eight mothers whose daughters had vaginal adenocarcinoma had taken estrogens in the early part of the pregnancy, while none of four matched controls for each patient had taken estrogens. Diethylstilbestrol, the synthetic estrogen, was shown to be the offending agent in the majority of cases.[179]

Statistical analysis indicated that the association of taking diethylstilbestrol during pregnancy and subsequent development of adenocarcinoma of the vagina in the daughters was highly significant ($p<0.00001$). Maternal bleeding during pregnancy and a history of involuntary abortion in a previous pregnancy were also significant factors. Smoking, exposure to x-rays, age, and breast feeding were not significant factors. Of eight women whose daughters had vaginal adenocarcinoma, there was only one who had neither taken stilbestrol during pregnancy nor had previous pregnancy loss. More, the tumors were known to occur rarely before the availability of estrogen therapy.[179] The stilbestrol used was taken during the years 1946-1951. During this interval 675 out of a total of 14,500 patients at a large women's hospital (a ratio of 1:21) had stilbestrol prescribed. From this, the risk factor would appear not to be very high although more and more cases are now being discovered.

The high prevalence of benign vaginal adenosis with these adenocarcinomas suggested that an anomaly of vaginal epithelium development might be a predisposing factor. An association between adenosis and clear-cell carcinoma of the vagina had previously been described in older women.[180] It was also suggested that the association of adenosis with the estrogenic effect of stilbestrol supported a Mullerian rather than mesonephric origin for these tumors. It was conjectured that the mechanism for the estrogenic induction of subsequent tumor in these patients might be either (1) that an increase in adenosis at menarche caused a predisposition to malignant change, or (2) that stilbestrol altered fetal vaginal cells, these changes manifesting as malignant disease years later. Finally, it was predicted that since estrogens were used widely in high-risk pregnancy during those years, it might be that increasing numbers of women with these tumors would be recognized as the at-risk population increased. In a further follow-up reported in 1972[181] these same investigators gave a fuller account of this tumor based on data from a registry that was established for the purpose of documenting the condition. Pregnancy histories were obtained on 66 of 91 cases in patients aged 8 to 25 years (mean age 17 years), and it was

learned that 49 of the mothers had received diethylstilbestrol or related drugs, nine had received other unidentified medications for bleeding or prevention of pregnancy loss, and only eight had had no recorded medication during pregnancy. A high incidence of vaginal adenosis in these patients was confirmed, which strengthened the suggestion that abnormal development of Mullerian epithelium was the focal point of origin for these tumors. Even though follow-up periods were brief, the data showed that 17 of 65 patients had died or had recurrence of the disease. The results of the investigations are summarized in Tables 20 through 22. Vaginal bleeding was again the most common presenting symptom (Table 21). However, 13 of 91 patients were asymptomatic and diagnosis was made by direct pelvic examination. In addition, vaginal cytologic examination was negative in nine out of 30 cases. The dose of drugs varied widely but it can be seen that none were of the steroidal varieties (Table 20); they were all synthetic estrogen-like compounds. The duration of drug therapy varied from 12 days to throughout term, and in all cases hormone therapy was started before the fourth month of pregnancy. The survival data are summarized in Table 22. Of 65 patients for whom data are available, 79 percent of those with vaginal carcinoma had survived, and 64 percent with cervical carcinomas had survived without recurrence. The follow-up period has been less than two years in many cases. It is to be noted that 26 percent of all patients had recurrence or died despite therapy (Table 22). The factors of size of tumor, depth of invasion and architectural pattern bore no statistically inordinate relationship to either node metastasis or survival. Mitotic activity, invasion of lymphatic channels and regional lymph node metastasis were important prognostic factors. The superficial location predominantly on the anterior vaginal wall was further evidence that the tumor was of Mullerian rather than mesonephric origin, since the mesonephric tumors occupy lateral or antero-lateral locations and are usually deeply situated.

As a result of these findings, screening programs have been set up in various centers in this country

TABLE 20.—*Data on Medication During Pregnancy of Mothers Whose Daughters Had Vaginal or Cervical Carcinoma in Their Youth**

Pregnancy Therapy	*Total Cases*	*Location of Carcinoma*	
		Vagina	*Cervix*
Stilbestrol	45	30	15
Dienestrol	2	1	1
Stilbestrol and dienestrol	1	1	..
Hexestrol	1	1	..
Medication for bleeding or previous miscarriage (type unknown)	9	4	5
None	8	4	4
TOTALS	66	41	25
History not obtainable	3	2	1
TOTALS	69	43	26
Investigation not complete	22		
TOTALS	91		

*Reprinted by permission from Herbst AL, et al: N Engl J Med 287:1259, 1972.

TABLE 21.—*Pre-therapy Symptoms and Result of Cytologic Examination**

Symptoms	*Number of Cases*	*Grade of Cytologic Smear*	*Number of Cases*
Bleeding or discharge	54	IV or V (positive)	11
Mass	1	IIR or III (doubtful)	10
None	13	I or II (negative)	9
Unknown	23	Not done	15
		Unknown	46
TOTALS	91		91

*Reprinted from Herbst AL, et al: N Engl J Med 287:1259, 1972

TABLE 22.—*Staging and Survival after Therapy**

Location of Cancer	*Number of Cases*	*Patients Living and Free of Disease* <2 yr	≥2 yr	*Patients with Recurrences*†	*Dead Patients*
Vagina:					
Stage I	28	14	12	2	0
Stage II	12	2	6	1	3
Stages III & IV	3	0	0	0	3
TOTALS	43	16	18	3	6
Cervix:					
Stage I	6	4	2	0	0
Stage II	11	6	0	1	4
Stages III & IV	5	0	2	1	2
TOTALS	22	10	4	2	6

*Reprinted from Herbst AL, et al: N Engl J Med 287:1259, 1972.

†Treated for or living with recurrence.

and internationally. The association between diethylstilbestrol ingestion in early pregnancy and the subsequent development of vaginal carcinoma in girls and young women has now been confirmed from a variety of centers in this and other countries.[182,183] It is clear that abnormal bleeding in adolescent girls must now be fully investigated, and that certain oral contraceptive agents play a role in the genesis of vaginal malignant disease.

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Refer to: Recent clinical and experimental developments in Sjögren's syndrome—Medical Staff Conference, University of California, San Francisco. West J Med 122:50-58, Jan 1975

Recent Clinical and Experimental Developments in Sjögren's Syndrome

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Assistant Professor of Medicine, and H. David Watts, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, CA 94143.

DR. SMITH:* *The subject of Medical Grand Rounds this morning is recent clinical and experimental developments in Sjögren's syndrome. As most of you know, this academic community has been one of the centers for the study of this very interesting disorder. We have turned to Dr. Norman Talal, Professor of Medicine and Chief of Rheumatology at Fort Miley Veterans Administration Hospital, to moderate this session. Dr. Talal has made many personal contributions in this field and is continuing his scholarship here. I would like to introduce him now to preside and to introduce the topic and the other speakers.*

DR. TALAL:† Thank you, Dr. Smith. Sjögren's syndrome is a chronic inflammatory and autoimmune disease characterized by the presence of dry eyes and dry mouth. Lymphocytic infiltration and destruction of the salivary and lacrimal glands is the hallmark of this disorder. About 30 percent of patients with rheumatoid arthritis have Sjögren's syndrome. Since there are between 3 and 4 million patients with rheumatoid arthritis in the United States, Sjögren's syndrome is by no means a rare disease.[1] Just over two years ago we established an interdepartmental cooperative study group in this medical center to evaluate patients with Sjögren's syndrome. The participants in today's Grand Rounds are the key members of this study group. To date, 110 patients have been evaluated by the techniques that will be discussed. Of this number, 80 patients have been diagnosed as having definite Sjögren's syndrome. Over half of the patients seen in our clinic have dry mouth and dry eyes without rheumatoid arthritis. These patients are especially prone to develop lymphocytic infiltrates in vital organs, such as kidney or lung, or even to develop malignant lymphoma.[2] The case for presentation today is an example of this type of lymphocyte aggressive disease occurring in the setting of Sjögren's syndrome. The patient will be presented by Dr. Jonathan Dixon.

DR. DIXON:‡ The patient for presentation today is a 76-year-old white woman, a retired school teacher. In about 1969 the onset of progressive

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symptoms of dry mouth, a burning and gritty sensation of the eyes, a burning sensation of the tongue and a rapid decay of teeth developed. The patient was told upon an evaluation at another hospital that her symptoms were due to the reserpine which she was taking for some mild hypertension. In February, 1971 she was referred to Dr. Sol Silverman in the Division of Oral Biology because of the increasing severity of these symptoms. On physical examination at that time, decreased tearing, dry mucous membranes, pronounced dental caries and angular cheilitis were noted. A clinical diagnosis of Sjögren's syndrome was made, and the patient was treated with various agents without relief of symptoms. Between that time and February, 1972 the patient had recurrent episodes of parotid swelling with intermittent episodes of purulent discharge that were treated with various antibiotics without significant improvement. In February, 1972 the patient was referred for the first time to the Sjögren's Syndrome Clinic. Review of systems at that time showed no symptoms referable to any underlying disorder associated with Sjögren's syndrome. A review of the medical history did show that there had been recurrent episodes of painless hematuria and of bacteruria and pyuria. Results of previous evaluations had included normal findings at intravenous pyelogram and cystoscopy; however, no renal function studies had been done.

On physical examination, swollen parotid glands bilaterally, a fissured tongue and submandibular adenopathy were noted. There was no evidence of pulmonary, joint or skin abnormalities. An ophthalmological examination was done at which a Schirmer's test showed no tear flow from either eye. A labial salivary gland biopsy specimen was taken and showed an intense inflammatory infiltrate with lymphocytes and plasma cells. Germinal center formation was evident on one section. Sequential salivary scintillographic studies showed no apparent uptake or concentration of technetium. In one section of the salivary gland biopsy specimen some normal glandular elements were seen, but most of the glandular elements had been replaced with a very dense infiltrate of lymphocytes and plasma cells.

In the Sjögren's Syndrome Clinic an extensive laboratory evaluation was done. Pertinent results included a sedimentation rate of 40 mm per hour, negative results from a lupus erythematosus (LE) cell test and findings showing that an antinuclear antibody (ANA) was present to a dilution of 1:16 with a speckled pattern. Results of a test for rheumatoid factor were positive to a dilution of 1:1,600, a Coombs' test produced weakly positive results, complement was normal and tests for antibodies for double stranded deoxyribonucleic acid (DNA) showed negative results on two occasions. Multiple analyses of the urine consistently showed trace proteinuria, one to two red cells per high power field, never any casts and a hydrogen ion concentration (pH) of 5. Urine light chains were found to be elevated on two occasions; one serum bicarbonate was 20 mEq per liter, but later determinations were all within normal limits. Blood urea nitrogen (BUN) was 24 and creatinine was 2.3 mg per 100 ml. At that time, x-ray films of the chest were normal. Studies of serum immunoglobulins showed a polyclonal increase in immunoglobulin G (IgG) to a level of 3,500 mg per 100 ml; there were normal concentrations of immunoglobulin M (IgM) and immunoglobulin A (IgA). Studies of peripheral blood lymphocytes using an immunofluorescent staining technique showed an increased percentage of cells staining for IgG and normal percentages staining for IgA and IgM.

Between February, 1972 and December, 1972 there were recurrent episodes of parotid swelling. This was again treated with various measures but without any relief of symptoms. In January, 1973 there developed, for the first time, symptoms of shortness of breath, dyspnea on exertion, cough and hemoptysis, as well as fever. The patient was seen by her private physician who treated her with antibiotics, but there was no relief of symptoms with this treatment. In March an x-ray film of the chest was taken which showed an infiltrate at the right base. The patient was referred back to us for further evaluation and treatment. Because of the x-ray findings and the symptoms, the patient was admitted to the University of California Medical Center on March 3. Physical examination at that time showed no change from results of earlier examinations, except for a few rales at both bases of the lung fields.

Pertinent changes or additions to the laboratory data were an increase in sedimentation rate to 77 mm per hour, an oxygen partial pressure (pO_2) of 60 mm of mercury, carbon dioxide partial pressure (pCO_2) 40 mm of mercury, BUN 28 and creatinine 2.3 mg per 100 ml. Creatinine clearance was 27 ml per min; 24-hour urinary protein was elevated on two occasions. Results of urinalysis at that time showed a pH of 5, 2 to 5 red cells per high power field and no casts. X-ray studies

of the chest again showed a right lower lobe infiltrate. Multiple examinations of sputum for cytology, Gram stain and culture were obtained but were not helpful in making any definitive diagnosis. Results of pulmonary function tests were completely within normal limits. Results of bronchoscopic studies were negative. Results of skin tests were all negative, except for a positive mumps skin test. Serum protein electrophoresis showed a pronounced increase in total protein with a polyclonal increase in the gamma globulin fraction to 5.0 grams per 100 ml. Immunoelectrophoresis again confirmed the polyclonal increase in the IgG. The patient was discharged from the medical center with the diagnosis of Sjögren's syndrome, pulmonary fibrosis secondary to the Sjögren's syndrome, as well as renal insufficieney of unknown ease.

Between March and May, 1973 there were increasing symptoms of cough and hemoptysis, and worsening pulmonary infiltrates. Because of the persistence of symptoms we decided to admit the patient to hospital again, this time at the hospital where we have most of our facilities, the San Francisco Veterans Administration Hospital. Results of laboratory tests and physical examination at that time were unchanged, except for chest x-ray studies which now showed extensive bilateral basilar infiltrates. The diagnostic choices facing us at that time were between an open lung biopsy or a renal biopsy and, for reasons which I think will become evident in Dr. Talal's discussion, we decided to do a renal biopsy. This was done by Dr. James Hopper. The biopsy specimens obtained showed changes consistent with interstitial nephritis of Sjögren's syndrome. Dr. Hopper will discuss these findings. The patient was discharged from the San Francisco Veterans Administration Hospital with the diagnosis of Sjögren's syndrome associated with lymphocytic infiltration of the lungs and interstitial nephritis (pseudolymphoma). Administration of chlorambucil (4 mg a day) was begun. In August, 1973 chlorambucil was stopped because of significant bone marrow suppression, and at that time the patient refused any further therapy.

Between August and December symptoms of cough, hemoptysis, shortness of breath, dyspnea on exertion, significant weight loss and considerable fatigue had increased notably. There was no change in the laboratory data, except for a steadily increasing IgG to a level of 7 grams per 100 ml, still polyclonal. Increasing pulmonary infiltrates were seen on an x-ray film of the chest and for the first time there was evidence of restrictive lung disease on pulmonary function tests. In January, 1974 the patient was admitted to hospital elsewhere for an episode of bronchopneumonia. Treatment with antibiotics brought resolution of the acute symptoms of fever and increased cough. Cytologies done there showed sheets of lymphocytes in the sputum. In February, 1974 the patient was started on prednisone (30 mg daily) and over the next four months there was pronounced symptomatic improvement with decreased cough and almost complete disappearance of hemoptysis and shortness of breath. The pulmonary infiltrates seen on x-ray films of the chest have decreased. There has been no change in renal function. The gamma globulin has decreased to 2.9 grams per 100 ml. There has been some increase in tearing and some increase in the amount of saliva.

DR. TALAL: This case demonstrates the type of lymphocyte infiltrative or lymphocyte aggressive disease with systemic complications that we see occasionally in patients with Sjögren's syndrome.[3] Dr. Dixon indicated that we are faced with a choice of which tissue to biopsy, the lung or the kidney. Based on experience with other patients of this sort, plus the fact that Dr. Hopper was available to do the kidney biopsy for us and the relative ease of that procedure compared with a lung biopsy, we elected to do the kidney biopsy. I would like to ask Dr. James Hopper to discuss those findings.

DR. HOPPER:* Thank you Dr. Talal. I should comment first that when we do a kidney biopsy, we routinely take two cores of tissue. We take them from different segments of the same kidney going through the same skin incision. We routinely do light, fluorescent and electron microscopy. In this case the fluorescent microscopy showed no evidence of precipitated fluorescence with IgG, IgA, IgM or complement. The light microscopy showed tubular degeneration, extensive fibrosis throughout and cellular infiltrates. The cells were plasma cells, lymphocytes and fibroblasts. There was much connective tissue between the tubules. When renal tubules atrophy, the glomeruli furnishing those tubules undergo sclerosis. The biopsy specimen from this patient showed quite a few sclerosed glomeruli, but we think these are secondary changes. The electron microscopy studies

*James Hopper, MD, Professor of Medicine.

were not particularly abnormal. The main abnormality seen by electron microscopy was the presence of so-called virus-like particles in the capillary endothelium. Virus-like particles are seen in the collagen diseases and in transplanted kidneys.

DR. TALAL: There are several points to be emphasized about this patient. Sjögren's syndrome is related to rheumatoid arthritis and systemic lupus erythematosus and, of course, renal involvement is very common in the latter. The renal involvement in lupus erythematosus is an immune complex problem in which circulating immune complexes (particularly DNA-antiDNA), along with complement are deposited in the glomeruli giving rise to a very active glomerulonephritis. This we do not generally see in Sjögren's syndrome. The renal involvement in Sjögren's syndrome is primarily one of direct cellular infiltration with lymphocytes and plasma cells. Rather than presenting as a nephritis, it generally presents as a tubular disorder with renal tubular acidosis.

This patient started with a fairly classical Sjögren's syndrome. At first there were the sicca symptoms of dry eyes and dry mouth but then features of extrasalivary involvement developed, particularly in the kidney and lung. Two events were occurring at the same time: (1) increasing lymphocytic infiltration, at one point producing sheets of lymphocytes in the bronchial washings, and (2) a continual and progressive increase in the production of immunoglobulins, particularly IgG. As we monitored immunoglobulin levels at intervals of a month, six months or a year, we witnessed their continued increase. In my later presentation when I discuss some of these features in detail, I will emphasize that this seems to be a disorder in which B lymphocytes (or bone marrow derived lymphocytes), which produce immunoglobulins, escape from a regulation exerted by the thymic derived or T lymphocyte population. We are seeing in this patient the overactivity and continual proliferation of immunoglobulin-producing cells.

The oral manifestations of Sjögren's syndrome can be extremely distressing and are often the patient's chief complaint. Many patients are first diagnosed by a dentist or otolaryngologist who was consulted because of a dry mouth. Dr. Troy Daniels, from our dental school, has contributed greatly to our understanding of the oral features of Sjögren's syndrome. Dr. Daniels wrote his thesis on this subject and is our next speaker.

DR. DANIELS:* I would like to discuss the clinical features of the oral aspects of Sjögren's syndrome and the diagnostic tests which we use in evaluating patients with this condition at this center. There is no single criterion which alone will establish the salivary involvement of Sjögren's syndrome. As with other conditions, a combination of history, physical examination and laboratory studies are necessary to evaluate each patient.

The oral signs and symptoms are related to the reduced production of saliva. The major cause of this reduced production of saliva is the tremendous infiltration of lymphoid cells into the organs. Some patients will mention that they have insufficient saliva or that they have a dry mouth. However, many patients will have a more indirect complaint such as difficulty in swallowing, usually attributable to the oropharyngeal region as opposed to esophageal difficulty. Some will note problems with dentures. Some will need very frequent rinsing to the extent that they may have to carry a small container of water. Some patients will complain of a reduction in their sense of taste. We have even had a few patients who have totally lost their sense of taste for a period of time. Many will complain of an inability to eat dry foods. On asking a patient whom you suspect of having Sjögren's syndrome if he or she can eat a dry cracker without the benefit of any fluid, a very strong negative response may be elicited. This has been called the positive "cracker sign" of Sjögren's syndrome. Many of the patients will relate a recent increase in incidence of dental caries. They may suddenly notice large numbers of decayed teeth, with the decay progressing very rapidly. Importantly, some patients present no complaint at all. Even in the face of pronounced salivary dysfunction they may not have any complaint, demonstrating the highly subjective nature of these problems. About one third of the patients will complain of recurrent grandular enlargement and may relate that they had mumps several times as an adult. About one third of the patients will present with frank glandular enlargement.

The presenting physical findings include parotid enlargement in approximately one third of the patients. It may be unilateral, but usually both glands become involved at some time or another. These masses can wax and wane and on palpation they are fairly firm, especially compared to similarly shaped enlargements which we see in sar-

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coidosis, diabetes mellitus or virus infections. Submandibular gland enlargement occurs less frequently than parotid enlargement; it is seldom visible, and one must palpate for it very carefully.

Intra-orally, the mucosa is characterized by a velvety appearance and may adhere to the finger when making the examination. The tissues can be so dry that they almost resemble parchment, and the absence of pooled saliva on the floor of the mouth is very obvious. These patients develop a different distribution of dental caries in which the cervical areas of the teeth adjacent to the gingiva and the incisal edges of the teeth decay first. These are normally not caries-prone areas but are the first to decay in patients with chronic xerostomia. Another common finding in patients with chronic xerostomia, particularly with Sjögren's syndrome, is a relative loss of the filiform papillae of the dorsal tongue. This causes the tongue to appear shinier and smoother than normal, and there is associated deep fissuring and relative erythema. The chronic xerostomia can alter the oral flora to such an extent that fungal organisms, particularly Candida albicans, flourish causing severe symptoms in patients. These symptoms are not relieved until the fungal infection is adequately treated.

We have used three laboratory methods to evaluate patients with Sjögren's syndrome. The first of these is to determine, using a standardized procedure, the secretory flow rate of the parotid glands. We use a Carlson Crittenden cup which is held over the parotid duct by negative pressure applied to the outer ring. The saliva is allowed to flow passively through the center chamber while a taste stimulus is applied to the tongue over a standard distribution. In results from a series of 64 normal persons the range of flow rates is 5 to 20 ml per ten minutes per gland. The normal rate is somewhat related to age. The greatest reduction is in those patients with Sjögren's syndrome without an associated connective tissue disease (mean of 1.2 ml per ten minutes per gland). These patients are generally quite symptomatic. Those patients with an associated connective tissue disease and Sjögren's syndrome have a less severe but still significant reduction of flow.

Another method for assessing salivary function is sequential scintillography as done by the Nuclear Medicine Division of this center.[4] Five millicuries of sodium pertechnitate are injected intravenously and the patient's neck placed in the extended position beneath a gamma camera. Photographs of the scintillographic display are then taken serially over a period of time. After eight to ten minutes, there is virtually maximal uptake in normal thyroid, submandibular and parotid glands bilaterally, and already some excretion into the mouth is visible. Up to 60 minutes, there is an increase in the excretion of the label into the mouth. In a patient with pronounced impairment of parotid function due to Sjögren's syndrome there is absolutely no uptake or concentration of the radio-label in any of the salivary regions, even after one hour. This test is very useful in evaluating more severe patients, but it is not sufficiently sensitive to be of great value in evaluating earlier and less severe cases.

Histological evaluation in salivary tissue is an important part of the workup in a patient suspected of having Sjögren's syndrome.[5] Because of the hazards of parotid surgical procedures, we are reluctant to biopsy that tissue. However, accessory salivary glands are present immediately beneath the labial mucosa and offer an effective alternative. We can use these tissues in lieu of doing salivary gland biopsy, a potentially complicated procedure. Under local anesthesia a linear incision in the labial mucosa reveals the glands immediately beneath that surface. By blunt dissection we can free them from the margins of the epithelium and underlying structures, remove them individually and process them for routine histopathology, for electron microscopy or immunofluorescent studies. The normal histology of a labial salivary gland consists of numerous mucous-type acini with a bit of stroma and scattered diffuse inflammatory cells usually between the acini but not in focal accumulations (Figure 1).

However, in Sjögren's syndrome focal accumulations of these lymphoid cells are characteristic and consist of lymphocytes and plasma cells (Figure 2). The smallest foci generally surround capillaries and then enlarge to engulf the ducts. Foci can become so numerous and large as to become confluent. Some ducts may remain but we frequently observe total replacement of the acini by lymphoid cells. Previous studies have shown that the focal accumulations of lymphoid cells are an infrequent finding in the normal labial salivary gland but a very consistent finding in Sjögren's syndrome. These changes also correlate with histopatholic findings in the major salivary glands from the same patients. This has let us to use a semiquantitative analysis of these histological findings according to a modification of the Chisholm and Mason criteria. By this method the number of in-

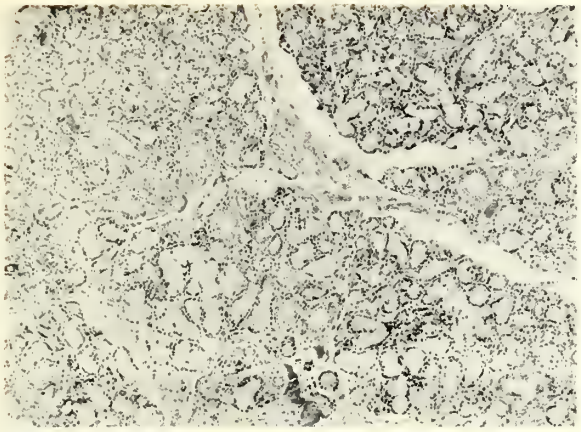

Figure 1.—Biopsy specimen of labial salivary gland from a normal adult.

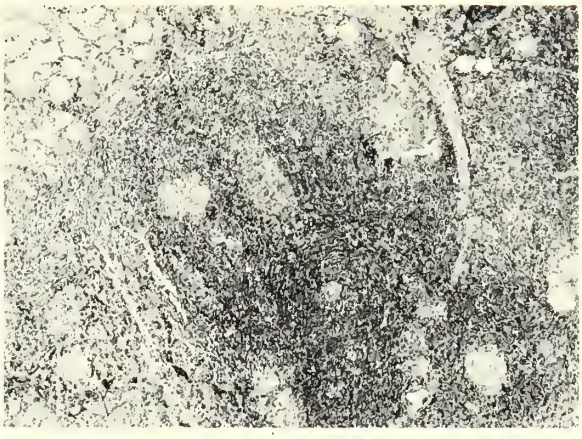

Figure 2.—Biopsy specimen of labial salivary gland from patient with Sjögren's syndrome and the sicca complex.

flammatory foci are counted and then related to a standard area (4 square mm) of gland section. It provides us with a score of the number of foci per 4 square mm of gland section. The highest focus scores are seen in those patients with the sicca complex, the same patients who are also the most symptomatic. We are inclined to question the diagnosis of Sjögren's syndrome in the absence of histological evidence. In those patients with an associated connective tissue disease, we see lower but still very significantly elevated focus scores. In controls of patients with connective tissue disease only, we see insignificant focal infiltration.

In closing, I might relate that therapy for the oral component of Sjögren's syndrome consists mainly of preventing the dental destruction that accompanies the chronic xerostomia and of providing the patient with symptomatic relief.

DR. TALAL: The keratoconjunctivitis sicca of Sjögren's syndrome may first bring the patient to the attention of an ophthalmologist. Henrik Sjögren himself was a Swedish ophthalmologist who first described the triad of dry eyes, dry mouth and deforming arthritis that bears his name. His description was recorded about thirty years ago. Dr. Bruce Ostler is an authority on this aspect of Sjögren's syndrome and is our next speaker.

DR. OSTLER:* To understand the problems of keratoconjunctivitis sicca, we should discuss the physiology of the precorneal tear film. Classically there are three layers to the precorneal tear film. The outermost layer is an oily phospholipid layer. The second layer is aqueous and the third is a mucoid layer. This type of classification allows one to consider the various types of dry eye syndromes and their treatments. The outer layer, the phospholipid layer, is produced by meibomian glands. In each eyelid there are 40 to 50 meibomian glands which secrete an oil which helps to retard evaporation of the tear film and reduces the surface tension allowing better spread of the aqueous tears themselves. This oily layer can be decreased. We mostly see decreased oily layers in cases of erythema multiforme with mucous membrane involvement or in Stevens-Johnson syndrome. One can recognize this by looking at the orifices of the glands. If they are scarred, one can conclude that the oily layer will be lost. The treatment of this is simple since one merely needs to use an occasional drop of castor oil or mineral oil. The oily layer is usually not altered in Sjögren's syndrome.

However, the middle or aqueous layer is definitely and frequently involved in Sjögren's syndrome. This middle layer functions to provide a smooth optical surface for vision and more importantly a proper milieu for the integrity of the epithelial cells of the conjunctiva and cornea. In its absence, the cornea, the cells lining the cornea and the conjunctiva begin to keratinize and take on the character of skin. This middle aqueous layer is secreted by the lacrimal glands and the accessory lacrimal glands that are located in the conjunctiva. It does contain some proteins, albumin, a middle fraction and tear lysozyme. Tear lysozyme, we feel, is quite important in helping to diagnose Sjögren's syndrome. The albumin, the middle fraction and tear lysozyme help to decrease

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the surface tension and again help to maintain continuous film of tear. Deficiencies in this layer may be encountered in Sjögren's syndrome or in instances in which there is scarring of the mucous membrane, such as in trachoma. We also observe decreased lacrimal gland function with medication (atropine, L-dopa) and with malnutrition. We measure the deficiency by the Schirmer tear strip which is commercially available. One merely has to place this strip medially into the conjunctival sac and measure the flow over a five-minute period. Normally there will be at least 10 mm of wetting in a five-minute period. The function of the basic secreters, the accessory lacrimal glands in the conjunctiva, is measured by anesthesizing the conjunctiva with a topical anesthetic and then instilling the Schirmer tear strip. This then detects only that aqueous material secreted by the conjunctiva. The basic secreters are those responsible for the constant formation of tears and the lacrimal gland itself is called into play only when exposed to noxious stimuli, such as smog, dust irritation and heat; or during strong emotional reactions. Occasionally one will find a chronic conjunctivitis or chronic irritation that can also cause a decrease in the amount of aqueous material produced and thus simulate a true dry eye.

We treat conjunctivitis sicca by replacement of the aqueous layer, such as with artificial tears. There are two types of artificial tears available. One type is that with methylcellulose as a base and the other is that with polyvinylpyrrol as a base. Neither works particularly well, but they do provide some help. One can also attempt to protect the evaporation or the loss of tears. The puncta can be closed quite easily to maintain tears in the conjunctival sac. Lid adhesions also prevent evaporation. The use of moisture shields on glasses often prevent evaporation and thus are helpful. The eye can be covered at night with a shield to prevent evaporation. Another important factor is humidification of the house. A person who lives in an air conditioned house and rides in an air condtioned car frequently becomes very symptomatic. Humidification can help considerably.

The tear lysozyme is a very important component of aqueous tears which we can measure readily in the laboratory. One merely collects the tears on a Schirmer tear strip or in the form of a tear drop, and lysozyme is detected using the Micrococcus, a microorganism which is very sensitive to tear lysozyme.

The innermost tear layer, the mucus layer, is derived from the goblet cells of the conjunctivae and from the lacrimal gland. Surprisingly, as Sjögren's syndrome progresses an excess of mucus accumulates, but it is an abnormal type of mucus and does not allow for the spread that is necessary. The mucus itself has two components: one is hydrophobic and thus resides against the corneal epithelium and the other is hydrophilic and interfaces with the aqueous portion of the tear. This is like having an oil spot on one's windshield. There may be plenty of water present on the windshield, but it just does not cover the oily spot. As far as the corneal epithelium is concerned, water, or the aqueous component, will not cover unless an intermediary is present, namely the mucus. This mucus also tends to disappear early in Sjögren's syndrome and thus creates a problem.

Blinking is an important process which helps to stir this up and keep the molecules in a proper alignment. We see the deficiency in Sjögren's syndrome, in siccatrizing diseases such as Stevens-Johnson, in trachoma and so forth. Treatment of this phase includes the use of mucomimetic drugs. We have even used serum albumin and 6-percent dextran, neither of which is fully satisfactory. The patient with a dry eye syndrome will usually present with either a foreign body sensation, itching or even excessive secretion and tearing. In this situation, there is a decreased mucus component and a compensatory increase in tear production. Other symptoms include inability to tear, blurring of vision, photophobia, pain, difficulty in moving the lids and redness. One will find an absence of a tear meniscus. Normally there is a small amount of tear meniscus which accumulates along the lower lid margin and is readily appreciated. Tenacious mucous threads which hang onto the cornea, conjunctival hyperemia and edematous folds of the conjunctivae, and even some redness of the lid margin itself, will often suggest a diminished mucus component. There may be destruction of the corneal epithelium itself. Corneal filaments which are true epithelial filaments may also be present.

One of the tests which will be most valuable for the internist is that of the Rose Bengal dye. Rose Bengal instilled into the conjunctival sac will stain areas in which there is loss of epithelium or abnormal epithelium. Extension of staining onto the cornea is definitely abnormal and frequently seen in Sjögren's syndrome. The complications of the dry syndrome are usually those of corneal ulcera-

tion, corneal vascularization, corneal perforation and corneal scarring. In addition, these patients are subject to frequent infections. Bacterial and viral infections are frequent because the tear flow is reduced.

DR. TALAL: Current hypotheses about the pathogenesis of autoimmune disease center around two basic concepts: (1) that these are examples of so-called slow or latent viral disease and (2) that these are examples of disordered immunological regulation. Obviously these two hypotheses are not mutually exclusive. We have attempted to gain experimental information on these points using labial salivary gland biopsy material obtained from our patients. We have collaborated in these studies with Dr. Natalie Kremer who is a research specialist in the Viral and Rickettsial Laboratory in the California State Department of Health. These experiments have not given evidence favoring a viral mechanism.[6]

Another approach in our investigative work has been to analyze the nature of T and B lymphocytes in the peripheral blood and tissue lesions of patients with Sjögren's syndrome.[7] Lymphocytes can be divided into two major classes—the so-called T or thymic-derived cells and the B or bone marrow-derived cells. All lymphocytes arise from a common origin as bone marrow stem cells and from this common origin take one of two pathways. They may peripheralize directly and appear in the so-called B cell dependent areas of lymph nodes, spleen and peripheral blood. The B cells mediate aspects of humoral immunity, are concerned with the production of antibody and are readily detected by the presence of surface immunoglobulins. In the patient under discussion today you heard that great quantities of immunoglobulins were being synthesized and there was a modest increase in peripheral blood B cells. The other pathway of differentiation of lymphocytes is to migrate through the thymus where lymphocytes come under the microenvironmental influence of the thymus gland. They then leave the thymus to occupy the so-called T or thymic-dependent areas of the peripheral lymphoid organs. In the peripheral blood about 70 to 75 percent of lymphocytes are T cells. These cells do not have detectable surface immunoglobulin by ordinary methods and have a totally different function in the immune response. They are primarily concerned with aspects of cellular immunity and mediate this function through the production of soluble factors or lymphokines. The lymphokines include migration inhibitory factor (MIF), blastogenic factor and cytotoxic factor. Although they do not have detectable surface immunoglobulins they have another surface antigen, an allo-antigen, best characterized in mice where it is called theta.

A number of laboratories are now developing antisera to detect a theta-type antigen or human T cells. I would like to distinguish T effector functions from T regulatory functions or the ability of T cells to influence the activity of B cells. These T regulatory functions can be considered as a kind of cooperation. The first described and best known was a helper activity in which T cells were necessary for maximal production of antibody by B cells. That is an example of a positive kind of cooperation. More recently we have become aware of a negative kind of cooperation in which T cells are said to exert a suppressor function on certain aspects of B cell activity. It seems quite reasonable now that all of us are predisposed to the formation of autoantibodies. We all have B lymphocytes capable of responding to autoantigens. The mechanism that prevents us from developing autoimmunity or autoimmune disease is at least in part dependent upon a surveillance mechanism expressed at the level of the T cell and mediated through this T suppressor activity. Our current concepts about Sjögren's syndrome center around a deficiency of T suppressor cells thereby allowing B cells to proliferate in an uncontrolled fashion and to continue making aberrant immune responses detectable as autoantibodies.

The immunological abnormalities in Sjögren's syndrome include a diffuse hypergammaglobulinemia, generally polyclonal, and frequently involving all immunoglobulin classes. When a monoclonal disorder occurs in the setting of Sjögren's syndrome, in our experience it has always involved the IgM. In other words, it has been coexisting Waldenstrom's macroglobulinemia and Sjögren's syndrome. In patients with such a disorder, great quantities of various types of autoantibodies, such as rheumatoid factor and antinuclear factor, are produced. Characteristically, the anti-double stranded DNA antibody seen in systemic lupus is not produced, and this may relate to the fact that renal disease in such patients is different from what one sees with lupus erythematosus. An antibody specific for salivary duct epithelium, detectable by fluorescent microscopy, is also produced.

The characteristic histopathological lesion is one of pronounced infiltration of the exocrine glands and presumably also of the kidney and the lung when these latter organs are involved. The circulating and infiltrating lymphocytes synthesize excessive quantities of immunoglobulin. This is an indication that B lymphocytes are present in the lesions. They synthesize great amounts of IgG and IgM and lesser amounts of IgA, the latter being the major salivary immunoglobulin. This indicates that these B cells probably arise in peripheral organs, such as the lymph node and spleen, and then attack and infiltrate the salivary glands, rather than arising in situ. If the latter were the case, we would expect to see predominately IgA production.

In collaboration with Dr. Ralph Williams, we were able to demonstrate that T lymphocytes are also present in the salivary gland infiltrates. We are dealing, therefore, with a mixed T cell-B cell lymphocyte infiltrative process which has certain important implications when one considers the mechanism whereby lymphocytes produce tissue destruction. Each of these lymphocytes would operate through a different mechanism. The peripheral blood of patients with Sjögren's syndrome shows a modest increase in peripheral blood B lymphocytes, and in about one third a modest decrease in peripheral blood T lymphocytes is shown. In addition to the local production of IgM and IgG, the infiltrating lymphocytes in the salivary glands are also producing autoantibodies such as rheumatoid factor.

Thus, the findings in the labial salivary glands in Sjögren's syndrome are remarkably analogous to the findings in the rheumatoid synovium. The rheumatoid synovium is infiltrated to a great degree by lymphocytes of both classes (B and T cells). There are excessive quantities of immunoglobulin being produced and, of course, rheumatoid factor is being produced and spills over into the synovial fluid. Sjögren's syndrome is related, as we have said, to the connective tissue diseases: rheumatoid arthritis, lupus erythematosus, polymyositis, scleroderma and periarteritis. There is about a 5-percent overlap with Hashimoto's thyroiditis, a very interesting analogy in terms of the histopathology of the salivary gland and the thyroid in these two conditions. There is perhaps a 10-percent or more overlap with chronic hepatobiliary disease. About 10 or 20 percent of patients with hyperglobulinemic purpura (nonthrombocytopenic purpura) of the lower extremities have Sjögren's syndrome. With regard to the lymphoid malignancies, a variety of lymphomas have been seen in patients with Sjögren's syndrome, most commonly reticulum cell sarcoma.

One can almost distinguish three stages of this disease, progressing from the most benign to the most malignant.[8] Stage 1 we call classical Sjögren's syndrome—the triad of xerostomia, xerophthalmia and rheumatoid arthritis. The pathological finding is one of benign lymphoid infiltrates confined to glandular tissues. Stage 2 we have called pseudolymphoma, and its features may include lymphadenopathy, enlargement and lymphocytic infiltration of the liver or spleen, nonthrombocytopenic hyperglobulinemic purpura, pulmonary lymphoid infiltrates and renal involvement secondary to lymphocytic infiltration. The histopathology is quite atypical and usually reported as an atypical lymphoid infiltrate. This lesion is very responsive to therapy. One would have to choose in any individual patient between corticosteroids or immunosuppressive drugs. The stage 1 lesion we treat very conservatively with replacement therapy such as eyedrops and fluids.

In some 1 to 2 percent of patients, there later develops a more fatal lymphocyte-aggressive disease sometimes characterized by hyperviscosity syndrome in the setting of Waldenstrom's macroglobulinemia or highly malignant reticulum cell sarcoma (stage 3). These lesions have been notoriously resistant to any attempt at chemotherapy or x-ray irradiation. Frequently in patients at this stage, autoantibodies are lost, immunoglobulins are lost and they actually become immune-deficient.

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Important Advances in Clinical Medicine

Epitomes of Progress—Obstetrics and Gynecology

The Scientific Board of the California Medical Association presents the following inventory of items of progress in Obstetrics and Gynecology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in Obstetrics and Gynecology which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Obstetrics and Gynecology of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, California Medical Association, 731 Market St., San Francisco, CA 94103

Current Concepts in Sterilization for Women

HUMAN STERILIZATION is the final step an individual can take to effectively prevent procreation. As it plays such a major role in fertility termination, sterilization must be an integral part of any family planning program. Over the last decade, voluntary sterilization has emerged from the mire of public unawareness and medically restrictive guidelines to become a widely used method of birth control throughout the world. Moreover, a number of new methods have been developed for simplifying surgical sterilization for women.

Classical methods of tubal ligation or standard gynecologic operations offer reliability, but little innovation. With the development of remote ("cold") fiberoptic light sources, separate pneumoperitoneum instruments and more sophisticated accessory equipment, transabdominal peritoneoscopy (laparoscopy) has provided a panoramic, laparotomy-like view of the pelvis. In the last two to three years, the impact of laparoscopy on gynecology has been tremendous. The most profound and prolific effect has been in the area of tubal sterilization, where laparoscopy has added rapidity, simplicity and, in many centers, an outpatient approach. The pregnancy rate (0.1 percent), following properly performed laparoscopic fulguration and tubal transection, is as good or better than that seen following classical tubal ligation. The overall complication rate varies from less than 1 percent to about 6 percent, although major complications are reported at a rate of approximately six per 1,000 (0.6 percent). Possibly the development of laparoscopic tubal clips or bands will eliminate some of the problems associated with electrocoagulation.

The ultimate goal is to reduce female sterilization to an office or clinic procedure not involving violation of the abdominal cavity, thus placing it in a position equal to vasectomy. A successful transuterine tubal sterilization method could be the answer, but hysteroscopic fulguration of the tubes

as they enter the endometrial cavity has not been a very successful, nor safe, technique. Until the transuterine approach is perfected, laparoscopic tubal sterilization should be advocated, offered and used by well-trained, competent gynecologists.

ROBERT ISRAEL, MD

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Status of Antihypertensive Therapy in Obstetrics

The traditional objective of antihypertensive therapy in pregnant patients has been to prevent the renal and cerebral sequelae that may result from hypertension. Recent animal experiments have shown a reduction in uterine blood flow during the acute phase of mild hypertension. This observation has serious fetal implications and may be related to the increased perinatal mortality and morbidity associated with gestational hypertension. Thus the choice of antihypertensive drug should take into account both maternal and fetal risks. While lowering the arterial pressure pharmacologically will protect the maternal cerebral vasculature, a further reduction in uterine blood flow may also occur which will further compromise the fetal environment.

Hydralazine, the drug of choice in many centers for the acute management of gestational hypertension, effectively lowers peripheral vascular resistance. In addition, it is known that hydralazine has a positive inotropic and chronotropic effect upon the heart resulting in an increased cardiac output. Studies in pregnant sheep have shown that the increased cardiac output increases the uterine blood flow significantly. This incremental flow to the uteroplacental circulation may be of great benefit to fetal welfare.

Hydralazine, therefore, should remain the drug of choice for acute gestational hypertension for both maternal and fetal indications.

CHARLES BRINKMAN, MD

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The Gravlee Jet Washer

THE GRAVLEE JET WASHER® is one of a number of devices available for increasing the yield of an endometrial sample. While not satisfactory as a method of assessing benign endometrial disease, it has proved successful in obtaining identifiable samples of the relatively viable cells of endometrial adenocarcinoma. When combined with endometrial biopsy, it provides a practical office method for assessing the possibility of endometrial adenocarcinoma in patents with perimenopausal bleeding.

One advantage of the jet washer is the fact that any desired amount of irrigating solution can be used with little or no danger of tumor dissemination because the fluid is circulated in a negative pressure system.

The tissue obtained is preserved by the addition of an equal volume of Papanicolaou fixative to the irrigating solution. From this a cell block is prepared to give a histologic specimen, which is superior to cytologic study.

While jet washing is a useful office procedure, it must be remembered that it is not as accurate as a diagnostic curettage. If one's index of suspicion is high, or symptoms persist, a negative report for cancer should be substantiated by a curettage.

LESTER T. HIBBARD, MD

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Audiovisual Techniques in Sex Education of Patients and Students

CERTAINLY MOST PEOPLE can derive benefit from a learning opportunity designed to clarify sexual and reproductive functions.

A curriculum prepared primarily for patients can be used for student instruction with relatively little modification. A variety of materials (for example, brochures, books, questionnaires, diagrams, plastic models, slides, films and audio and video tapes), if chosen carefully, can offer invaluable assistance to those engaged in the design and implementation of treatment programs for individual persons and couples with the complaint of "sexual dissatisfaction." Items selected should be evaluated periodically to ascertain their effective-

ness in treating such a condition. Among the key factors in selecting from available media are economic and spatial considerations.

For many persons seeking help, a clinician's permission to use carefully structured learning programs which provide limited information and offer specific suggestions, may be sufficient to alleviate, and in some instances eliminate, the presenting complaint.

RONALD J. PION, MD

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Catalog of the Multi Media Resource Center, San Francisco

Follow-Up of Molar Pregnancy

HYDATIDIFORM MOLE complicates about one in 1,500 pregnancies in the United States. Prediction of which 15 to 20 percent of these molar pregnancies will demonstrate malignant sequelae often cannot be based on histologic examination of the evacuated mole. For this reason it is of critical importance to follow *all* patients with serial chorionic gonadotrophin (HCG) assays, since this is a sensitive biologic marker of trophoblastic activity. In addition, periodic x-ray studies of the chest and pelvic examinations are important, since the lungs and vagina are the commonest sites of metastatic disease, and subinvolution of the uterus suggests persistent uterine disease.

There are several components to an acceptable follow-up program:

- An HCG assay done every one to two weeks using a sensitive serum radioimmunoassay until
  1. HCG is no longer detectable at sensitive levels for three consecutive determinations (patient has entered spontaneous remission). Follow with HCG assays every two to three months for one year.
  2. HCG plateaus are at an elevated level. Institute therapy.
  3. HCG rises significantly. Institute therapy.
  4. Metastases are detected. Institute therapy.
- Biweekly pelvic and physical examinations to rule out metastases and to note uterine/ovarian regression.
- Baseline chest x-ray studies for metastases; follow-up films if HCG does not steadily decline.
- Prompt institution of effective contraception, continued at least one year.

An essential aspect of proper follow-up is meticulous attention to the serial HCG titers.

WILLIAM E. LUCAS, MD

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Ultrasound in Obstetrics

THE ADVENT OF ULTRASOUND has been a major advance in fetal and maternal evaluation throughout pregnancy. It provides a safe and reliable method to obtain information that will be useful for the diagnosis and management of clinical problems.

The gestational sac can be visualized as early as the sixth week (counting from the last menstrual period), and its location is defined as intrauterine or extrauterine, thus diagnosing ectopic pregnancy. Two or more gestational sacs will indicate multiple pregnancy. The fetal head is well defined by 14 weeks and the measurement of the biparietal diameter will correlate with gestational age. This correlation can be improved by simultaneous measurements of the diameter of the fetal thorax. A biparietal diameter of 9.5 centimeters or more usually indicates a term fetus. This is useful in the clinical evaluation of patients with questionable dates, diabetes, erythroblastosis or hydramnios, or those scheduled for induction of labor or cesarean section.

Serial cephalometry may show accelerated growth suggestive of hydrocephaly, while slow growth provides a clue for intrauterine growth retardation. Failure to demonstrate a fetal head with repeated scans after the 14th week indicates anencephaly. An arrest of cephalic growth associated with loss of circular outline in both head and thorax, and failure to locate fetal heart beat with the ultrasonic Doppler, will diagnose fetal demise.

Placental localization is one of the most outstanding achievements of ultrasonic diagnosis. The location of the placenta by direct visualization and its relationship with the fetus and uterine

structures has obvious clinical significance in a situation like placenta previa or before amniocentesis. At the same time, structures, margins and surfaces can be evaluated with the gray scale technique for other types of placental pathology such as abruptio. Molar pregnancy can be diagnosed quite early since it produces a typical echo pattern.

HUGO RIFFEL, MD

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Ambulatory Surgical Gynecology

GYNECOLOGICAL SURGICAL PROCEDURES that are brief and low risk and for which postoperative care is simple (such as dilatation and curettage) may often be best done on a come-and-go basis in a surgical facility which has been especially designed for ambulatory patients. Such a facility may be developed in a physician's office, a clinic, a separate facility ("surgicenter") or a general hospital. It must be equipped to provide all the safeguards that are standard in a general hospital. The entire facility, its maintenance and its records, must be accessible for peer evaluation and review.

Whether general anesthesia or local anesthesia is used, the ambulatory surgical facility should provide adequately maintained monitoring and resuscitation equipment. Local infiltration or paracervical block anesthesia, possibly supplemented by intravenously administered diazepam (Valium®), is often satisfactory to both patient and physician. If general anesthesia is used, it should be professionally administered. Careful preoperative evaluation to insure low risk status and competent immediate recovery care must be provided. However, after the patient has recovered from general ansthesia, further postoperative care by loved ones in the familiar surroundings of home may be as safe and far more agreeable than the regimented professional routines normally provided by hospitals to inpatients.

Lesions of the vulvae, such as Bartholin cysts needing marsupialization, sebaceous cysts needing excision, suspicious skin or mucosal lesions needing biopsy, perineal stenoses needing reverse perineorrhaphy and even breast biopsies, may usually be managed satisfactorily under local anesthesia. Dilatation of the cervix, uterine curettage, difficult intrauterine device insertion or removal, cervical cauterization, superficial conization and menstrual extractions, may all be performed under paracervical block anesthesia using mepibacaine hydrocloride (Carbocaine®) and lidocaine. Laparoscopy and extensive cervical cold conizations on come-and-go patients are more commonly done under general (thiopental [Pentothal®]) anesthesia. Preoperative risk evaluation must always be done. Patients who are high in surgical risk due to advanced age, severe anemia or vascular diseases, should, of course, be admitted to a hospital for treatment.

PURVIS L. MARTIN, MD

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Lymphangiography and Cervical Cancer

THE IDEAL METHOD for the detection of lymph node metastases in patients with cervical cancer would be accurate, easy to carry out and easy to interpret, and would not require exploratory operation. Though lymphangiography does not meet all these requirements, it is better than any other available method. Negative lymphangiographic results are not of much value because (1) not all nodes in the pelvic and aortic areas are normally visualized and (2) metastases less than 3 mm in size are not seen as defects in the node. Nevertheless, when lymphangiograms give positive results (and are done by experts and evaluated using strict criteria), they are reliable. The finding of a lymph node filling defect not transversed by lymphatics is the most reliable criterion for identifying metastasis. Other findings such as lymphatic obstruction, collateral circulation or stasis may result from other causes and are not sufficiently reliable to be useful clinically.

Many centers employ lymphangiography as an orientation technique to be used for patients in whom routine surgical exploration with lymph node biopsy of lymphangiographic suspicious areas is to be done. Should biopsy specimens show the presence of metastatic carcinoma in aortic lymph nodes, treatment portals are enlarged to include

the para aortic nodal areas to the level of the 12th thoracic vertebra. Some patients in whom positive aortic nodes have been so treated are apparently living free of tumor, but further studies of larger numbers are necessary to determine how many patients will benefit from these additional measures. At present, lymphangiography in cervical cancer is most useful when other diagnostic and therapeutic steps, such as surgical staging and expanded aortic treatment fields, are available. Because of the urgent need for accurate information about lymph node metastases, efforts to improve the usefulness of lymphangiography should continue.

LEO D. LAGASSE, MD

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The Oxytocin Challenge Test

THE OXYTOCIN CHALLENGE TEST (OCT) is a method currently being used to evaluate uteroplacental respiratory function before labor. The test is done by recording fetal heart rate (FHR) and uterine contractions (UC) on a strip chart by means of a suitable external fetal monitor. The FHR response of late deceleration suggests uteroplacental respiratory insufficiency as shown by Hon and others during intrapartum fetal studies. Uterine contractions are known to interfere with uterine blood flow and are used in this test to provide an intermittant hypoxic stress to the fetus. If the FHR response to spontaneous or oxytocin-induced uterine contractions that are occurring at a frequency of three per 10 minutes shows no late decleration (negative OCT), the fetus is believed to be in little or no danger of intrauterine demise for one week following the OCT. When persistent late deceleration of the FHR is present the patient is said to have a positive OCT and one can no longer be assured that the fetus will survive continued intrauterine existence. If fetal maturity is likely (lecithin-sphingomyelin ratio, $L/S > 2.0$) delivery would seem advisable. However, it should be emphasized that the positive OCT does not always signify imminent fetal danger and one should use other methods to assess fetal well-being (for example, a 24-hour urinary estriol test) when the OCT is positive and fetal maturity is unlikely ($L/S < 2.0$).

The OCT gives rapid information about fetal well-being and has not been associated with an increased incidence of premature labor. It appears that the clinical value of the OCT is to allow one to avoid unnecessary premature delivery in patients at high risk for antepartum uteroplacental insufficiency.

ROGER K. FREEMAN, MD

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Cryosurgery

THE MANAGEMENT of benign diseases of the visible portion of the female genital tract has been significantly simplified following the introduction of cryosurgical therapy to the physician's armamentarium. Chronic cervicitis, that is, columnar tissue on the ectocervix, has been shown to respond favorably to outpatient cryotherapy with minimal complications. The success rate approaches 90 percent, and the technique is superior to hot cautery and avoids the hazards as well as expense of conization of the cervix. In fact, with the advent of cryosurgery, cervical conization is no longer warranted as treatment for "cervicitis."

When a physician desires to treat a patient with freezing for benign cervical disease, a Papanicolaou test must first be given and normal results obtained. Freezing is best done right after a menstrual period. During the treatment session, which is done without anesthesia or analgesia, it is most important that the iceball extend at least three to four millimeters onto healthy appearing tissue.

Cryosurgical therapy is also of benefit in the management of patients with resistant condyloma acuminata of the vulva, that is, non- or partially-responsive to podophyllin. When using the technique in a patient with vulvar condyloma acuminata, it is important to thoroughly freeze the base of the vulva but not an area greater than 2 or 3 cm in diameter in order to avoid excessive post-treatment complications.

The only significant sequela following cryosurgery has been a profuse watery discharge. Cervical stenosis and postoperative hemorrhage have not

been seen in any substantial number of patients.

Investigations are now being carried out using cryosurgery in the management of patients with cervical intraepithelial neoplasia, that is, dysplasia and carcinoma *in situ*. These studies are still investigational and must only be done by those who are experts in colposcopy.

DUANE E. TOWNSEND, MD

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Electronic Monitoring of the Fetus and Its Cost

FOR MANY YEARS fetal heart rate has been used as an indicator of fetal distress. Recent electronic advances make it possible for this to be done continuously rather than intermittently. The patterns of heart rate change elucidated by Hon enable the obstetrician to more adequately manage his fetal patient. This can be done at a relatively low cost (about $35.00). Some investigators have shown there to be a decrease in perinatal mortality coincident with the use of continuous fetal heart rate monitoring. Assuming fetal brain damage occurs before fetal death, one might anticipate a reduction in perinatal brain damage associated with continuous monitoring. If such a reduction occurs, it would more than compensate the cost to each patient.

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Menstrual Extraction

MENSTRUAL EXTRACTION is an office procedure for the evacuation of the uterus before a definitive diagnosis of pregnancy can be established by routine pregnancy tests. It is done usually between the 29th and 42nd day after the first day of the last menstrual period.

The technique is similar to that of a routine therapeutic abortion using suction curettage, except cervical dilatation is unnecessary. Oral analgesics or paracervical block or both can be administered just before the procedure. A small-diameter flexible polythylene cannula (4 to 6 mm Karman® catheter) can be used with either an electric vacuum pump or a hand operated syringe as a vacuum source. Completeness of evacuation can be confirmed by exploring the uterine cavity with a small metal curette. It is important that the patient be examined after two weeks and that a pregnancy test be made. A small percentage of pregnancies may be missed with this procedure.

The major disadvantage is that a certain number of women will be found not to be pregnant and therefore an unnecessary procedure will have been done.

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Luteinizing Hormone-Releasing Hormone as a Provocative Test of Pituitary Gonadotropin Function

NORMAL OVULATION is a result of a synchronization of the hypothalamic-pituitary-ovarian axis. Until recently the functional integrity of the hypothalamus and pituitary could not be evaluated separately. Determination of urinary or serum gonadotropin has served as an index of intactness of hypothalamic-pituitary function. Withdrawal bleeding following progesterone administration indirectly measures the functional integrity of the hypothalamic-pituitary-ovarian axis, although bleeding can occur even when the axis is operating in a dysfunctional manner.

In 1971 luteinizing hormone-releasing hormone (LRH), a hypothalamic hormone, was isolated, the structure determined and the compound subsequently synthesized. The availability of LRH has given the gynecologist a hormone which can measure the ability of the pituitary gland to synthesize as well as release luteinizing hormone (LH) and follicle stimulating hormone (FSH).

Patients presenting with amenorrhea should first be screened for genetic and endocrine causes other than hypothalamic-pituitary-ovarian axis

dysfunction. If these are ruled out, 100 μg of synthetic LRH is administered intravenously over a five-minute period. Baseline and serial blood samples are drawn over a two-hour period and subsequently assayed for FSH and LH. A significant rise in LH and FSH indicates an intact pituitary which is capable of responding to an appropriate stimulus. The interpretation of test results does not appear to be complex. It is anticipated that synthetic LRH will be clinically available in the near future. At that time its use should become a routine diagnostic and prognostic test in the evaluation of patients presenting with amenorrhea suspected to be caused by hypothalamic-pituitary-ovarian axis dysfunction.

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EDITORIAL

WJM Welcomes Idaho

It is just a year since California Medicine entered its chrysalis and emerged transformed into The Western Journal of Medicine. Long the voice of medicine in California, it aspired to become the voice of medicine in the West. The first issue of WJM in January 1974 noted that "The vitality and achievements in science, education and practice which are the hallmarks of medicine in the western United States now need a stronger presence in the medical literature which records and shares advances and progress with the medical community in the nation and indeed the world. The Western Journal of Medicine hopes to give medicine in the West this presence and this recognition." Physicians in the western states were asked to help in creating a truly regional journal.

The response has been gratifying. Respected physicians from throughout the West now serve as active members of the Editorial Board. Increasing numbers of articles of a high order of excellence and scholarship are being received from all parts of the region. And, to the publisher's satisfaction, perhaps even relief, the circulation figures for the western states have grown substantially.

This month another significant step is taken toward the Journal's goal. A resolution adopted last July by the House of Delegates of the Idaho Medical Association declared The Western Journal of Medicine, effective January 1, 1975, to be the official journal of the Idaho Medical Association. Starting with this issue, each member of the Idaho Medical Association henceforth will receive the Journal as one of the benefits of membership.

We welcome the physicians of Idaho, and we look forward to a long and productive association which should be of great benefit to all concerned.

—MSMW

Oral Contraceptive Agents

Approximately 20 million women throughout the world are now using hormonal contraception. Despite the effectiveness of birth control pills and their obvious value as a means of limiting population growth, their use in many countries is severely limited. In these areas physician resistance plays a part in nonacceptance.[1,2] In the United States there also are physicians who discourage women from using hormonal contraceptives. Too often their attitudes are based on individual experience with pill side effects without the perspective that collective experience brings. In this issue of the Journal, the symposium on complications of oral contraceptive agents performs a useful service by bringing together the best information available on the risks of oral contraception. Table 11 in the symposium, reprinted from an article by Goldzieher, places the discussion in perspective by emphasizing the lethal risks of pregnancy. The almost total effectiveness of the pill in preventing conception eliminates that threat. As to the risks of the drugs themselves, the symposium points out that there is no evidence connecting birth control pills with cancer of the breast, cervix or uterus. Despite assurances in this regard, there is still real concern over the metabolic effects of the drugs. The long-term consequences, if any, of changes in glucose tolerance and cholesterol and triglyceride levels are unknown.

On a very practical level the physician has only limited guidance in determining which women are not candidates for oral contraception. The symposium suggests that, among others, women with factors predisposing to thromboembolism should not be given oral contraceptives. They include women with congestive heart failure, a history of thrombophlebitis or embolism, significant edema, obesity or varicose veins. Excluding women in the latter two categories from the benefits of oral con-

traception is, in my view, too stringent a proscription. Similarly, the suggestion that a history of acute liver disease should preclude use of the pill may be overly stringent. However, a history of cholestatic liver disease is a definite contraindication to their use.

The use of oral contraception in the face of hypertension, diabetes or a strong family history of diabetes, remains a matter of judgment. The need for 100 percent contraception must be balanced against the risk. Frequent monitoring of glucose tolerance and blood pressure are necessary.

In women with strong family histories of coronary artery disease, it would be wise to obtain results of serum triglyceride, cholesterol and chylomicron tests before starting oral contraception and periodically during pill therapy. The symposium suggests that this be done in all patients regardless of familial history.

When prescribing the pill, the physician should alert the woman to symptoms suggestive of important side effects. These would include leg pain, swelling, redness, changes in visual acuity and persistent headaches. As with the others, the latter symptom is of great concern. There appears to be an association between oral contraceptives and lesions in the vertebrobasilar posterial cerebral arterial system.[3] Cerebral thrombosis occurring during pill usage is often preceded by migraine type headaches. Their presence suggests a need for switching to another pill for a brief trial or discontinuing hormonal contraception altogether.

Women taking oral contraceptives should be seen every six months for an interview, urine analysis and a blood pressure determination. Breast and pelvic examination with a Papanicolaou smear should be done yearly in the asymptomatic woman who has no significant history of disease and no significant family history of disease. The need for routine blood sugar, triglyceride and cholesterol testing in each of the 8 million women taking the pill in the United States is still to be determined.

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Health, Well-Being, Biological Systems and Ethics

THE GROWING INTERDEPENDENCE of almost every aspect of human society in the modern world is a fact of life with which we have yet to learn to cope effectively at any level of social organization or government. The evidence of this is everywhere about us. Both nationwide and worldwide are the rising expectations and social demands of the have-nots which no one seems to know how to meet. The economic system is producing a potentially devastating nationwide and worldwide inflation, and there is no agreement even among economists as to what can be done to correct or control it. And the political efforts to solve these and other problems of health and well-being for any nation, not to mention mankind as a whole, have generally been relatively ineffective and often have worsened the problems they sought to correct. The scholarly disciplines of sociology, economics and political science have so far failed to come up with adequate answers, and it seems quite evident that they are not yet sufficiently developed as professional disciplines to be of much real help.

It is suggested that many of the assumptions of the social sciences and consequently the findings upon which actions are based in both the public and private sectors may not be soundly based and that this may be because the true significance of the underlying biological nature of human life and human behavior in the earth's closed ecosystem has not yet been fully appreciated in these disciplines. The facts are that life on earth—including human life—finds itself part of a closed biosphere and thus subject to the laws of biological systems. Humans themselves are by their nature biological systems and, like all forms of life, their biological nature governs their behavior as individuals, their relationships to one another and their adaptation or lack of it to the environment in which they find themselves. Perhaps what is needed now is recognition of the biological nature of mankind and the probably biological nature of man's problems and development of a more bio-

logical base or framework for the social and behavioral sciences.

In any case the realities of the interaction of the closed biosphere with the human population on earth are becoming increasingly evident for all to see. For the first time in human history technologic progress has made it possible for the world population to increase enough to make the pinch of the closed biosphere felt in terms such as finite food and energy resources and an unhealthy technological pollution of the land, sea and air environment. In a very real sense the social, economic, political and legislative problems engendered by the effects of modern technologic progress—and inadequately dealt with by sociology, economics and political science at present—can be viewed as biological problems and studied within a biological framework. It seems reasonable to assume that just as human nature and human behavior are fundamentally biological, so are the social, economic and political systems of mankind. It is suggested that if this can be recognized and accepted it begins to be possible to think of the problems of mankind on earth in different terms. In such a context as this, health and well-being take on new meaning and the principle of adaptation of man and his environment for health and well-being takes on new dimensions. Man has developed considerable capability to influence his environment both favorably and unfavorably, and he has a considerably lesser—but still significant—capability to influence his own nature and behavior both individually and as a species. Both should be improved, but it is the latter capability which now sorely needs strengthening. This will almost certainly require new and more soundly biologically-based approaches within the social and behavioral sciences.

But still more will be necessary. Human behavior in adapting to the problems of the closed earth biosphere cannot be separated from ethics, from some consideration of what is right and what is wrong. There is no provision in natural law for right or wrong. If health and well-being, and improving something called the quality of life are to be accepted as principal goals of mankind on earth, then it may be possible, even necessary, to construct an ethic of right and wrong around these goals and do this within the framework of the natural law within which mankind must function within the earth ecosystem.

There is much to be done. It is important to note that health care is at the interface of health and well-being, or the lack of it, in any society. It is in health care that many of the unsolved problems of such a biological society as has been discussed come into the sharpest focus. If there is to be a better understanding of these problems and if better solutions are to be found, sophisticated input will be needed from both medicine and society—an input which neither is yet prepared to give.

—MSMW

Sjögren's Syndrome

In 1933, Henrik Sjögren, a Swedish ophthalmologist, published a classic monograph detailing observations on keratoconjunctivitis sicca, a condition characterized by dryness of the eyes. Sjögren's study clearly established that the ocular findings of this disorder were but a local manifestation of a more generalized disease process in which arthritis, anemia and other systemic features were present. The disease also included decreased secretion of the salivary glands and of the mucosal glands of the mouth and upper respiratory tract, and parotid enlargement. Subsequently termed Sjögren's syndrome, the condition is now recognized as a multisystem disorder intimately related to the various connective tissue diseases.

As indicated by Talal in the Medical Staff Conference on Sjögren's syndrome appearing elsewhere in this issue, the disease is by no means rare; indeed, it is the second most frequent collagen disorder, surpassed in prevalence only by rheumatoid arthritis. The diagnosis is, however, frequently overlooked. Whaley et al[1] recently observed that Sjögren's syndrome had been unsuspected before referral in all of 94 patients in whom it coexisted with rheumatoid arthritis, who were seen in a diagnostic center in Glasgow. Most of the referrals had been made by consultants, physicians who should probably have been conversant with the disorder.

Although an occasional person may be asymptomatic in spite of significant abnormalities of lacrimal and salivary glands, most persons with Sjögren's syndrome complain of discomfort and dryness of the eyes and mouth, and many note

abnormalities of smell and taste. That such symptoms may be overlooked or considered trivial in comparison with the serious joint disease or visceral involvement of their associated connective tissue disorder is understandable and may in part explain the frequent nonrecognition of the ocular manifestations of this disease. Anderson et al[2] have demonstrated that these manifestations are sufficiently distinctive that the diagnosis can be made with a high degree of accuracy by physicians who have no ophthalmologic training but are aware of the symptoms and physical findings.

Once the diagnosis is suspected, it may be corroborated by such procedures as the Schirmer test, ocular staining and measurement of tear lysozyme, as well as by the techniques that assess salivary gland function which are described by Daniels in the Medical Staff Conference. Diagnostic confirmation is best accomplished by microscopic examination of salivary gland tissue. The mucous glands of the lip are almost always involved in the polyglandular inflammation that characterizes Sjögren's syndrome; the labial mucosa is a preferred site for biopsy: here, removal of tissue causes minimal discomfort and entails minimal risk. The degree of lymphocytic infiltration is quantifiable, and has been shown to correlate well with clinical manifestations and objective measures of disease severity.[3,4] Since this technique has come into use, biopsy of the parotid and submandibular glands is seldom required.

In addition to broadening our understanding of the nature and spectrum of Sjögren's syndrome, early diagnosis has practical value. The institution of simple measures such as artificial tears and careful dental prophylaxis often averts serious ocular complications and preserves dental integrity. Establishing the diagnosis alerts the physician to anticipate some of the potential complications and may enable him to deal with them earlier and hence more effectively. Among these are renal tubular acidosis, chronic interstitial disease of kidney and lung, pancreatitis, vasculitis, recurrent respiratory infections, hyperviscosity syndrome and the development of lymphoma and macroglobulinemia.[5]

The association of Sjögren's syndrome with rheumatoid arthritis is well known. When large series of patients with rheumatoid arthritis have been screened for Sjögren's syndrome, the coexistence was noted in a significant minority, and varied directly with the severity and duration of the rheumatoid condition. The first systematic investigation for an association with other collagen diseases is that recently embarked upon by Alarcón-Segovia and coworkers.[6-8] They looked first for an association with primary biliary cirrhosis because it, like Sjögren's syndrome, has elements suggesting an immunologic imbalance, and because its coexistence with Sjögren's syndrome had been observed. In all of 14 consecutive patients with biopsy-proved primary biliary cirrhosis, the criteria for the diagnosis of Sjögren's syndrome were satisfied.[6] Similar investigations have now been reported in unselected series of patients with scleroderma[7] and systemic lupus erythematosus.[8] Surprisingly, in these series also, both clinical and pathologic evidence of Sjögren's syndrome was found in almost every patient examined. This frequency far exceeds that observed in rheumatoid arthritis, albeit the disease state in patients with systemic lupus erythematosus or scleroderma tends to be milder and is often subclinical. There is no clear explanation for the remarkable frequency with which these disorders and Sjögren's syndrome coexist.

Most probably the clarification of the reasons for this striking association, and of other puzzling aspects of these disorders such as the heightened incidence of neoplasms and the immunologic aberrations must await better understanding of the causes and pathogenesis of the various connective tissue diseases. Interdisciplinary investigative activities of the type described by Talal and other members of the study group in this Medical Staff Conference can be expected to yield information of the kind that is required before such questions can be answered.

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CASE REPORTS

Refer to: Wyler DJ, Glickman MG, Brewin A: Persistent serratia bacteremia associated with drug abuse. West J Med 122: 70-73, Jan 1975

Persistent Serratia Bacteremia Associated with Drug Abuse

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INFECTIONS resulting from illicit intravenous use of drugs, often with unusual pathogens and manner of presentation, are becoming increasingly common.[1] We report an unusual case of persistent bacteremia, caused by Serratia marcescens and complicated by the development of mycotic aneurysm, in a patient using methylphenidate hydrochloride (Ritalin®) intravenously. "Total body" arteriography identified the occult septic foci in this case of bacteremia that was refractory to aggressive antibiotic therapy.

Report of a Case

A 47-year-old Causacian man entered the hospital after one week of symptoms, including dyspnea, arthralgias, myalgias, and hematuria. For five years, the patient had been injecting himself with nonsterile solutions of filtered, pulverized methylphenidate hydrochloride. He had had multiple episodes of fever, chills, and hematuria that had required admission to hospital. Acute glomerulonephritis of nonstreptococcal origin was diagnosed on at least one occasion; bacteremia was at no time documented.

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On admission, the patient appeared acutely ill. The blood pressure was 130/75 mm of mercury, the pulse was 100 per minute, and rectal temperature was 39°C (102.2°F). His skin had "needle tracks" without evidence of inflammation, and petechiae were noted on the left thigh. No splinter hemorrhages, Osler's nodes, Janeway's spots, or Roth's spots were present. There was bilateral costovertebral angle tenderness to percussion. The rest of the physical examination was entirely within normal limits.

The hematocrit was 29 percent and leukocytes numbered 12,600 per cu mm with a normal differential count. Urinalysis showed isosthenuria and gross hematuria without cylindruria or proteinuria; serum electrolytes were normal except for moderate hyponatremia and hypochloremia. Blood urea nitrogen was 44 mg per 100 ml, serum creatinine was 2.9 mg per 100 ml, and creatinine clearance was 11 ml per minute. Roentgenograms of the chest and abdomen and an electrocardiogram were essentially normal. Six blood cultures were obtained, and the patient was given cephalothin (1 gram intravenously every six hours) and kanamycin (a single 1-gram dose intramuscularly) on an empirical basis.

On the following day, all blood cultures yielded Serratia marcescens, which was sensitive to chloramphenicol, kanamycin, gentamicin, and carbenicillin. Urine cultures grew approximately 5,000 colonies of S. marcescens with the same spectrum of antibiotic sensitivities. Sputum cultures grew normal oral flora. Gentamicin (80 mg intramuscularly three time daily) and carbenicillin (a 30-gram loading dose followed by 5 grams intravenously twice daily) were administered, and cephalothin and kanamycin were discontinued. Dosages and schedule were altered in line with the results of serum bactericidal determinations and drug synergism studies, as well as the patient's changing renal function.

On the second hospital day, petechiae in the conjunctiva of the left eye were noted for the first time. During the next 48 hours, pronounced chemosis developed, and full-blown endophthalmitis followed. Intraconjunctival injections of gentamicin and steroids arrested the local infec-

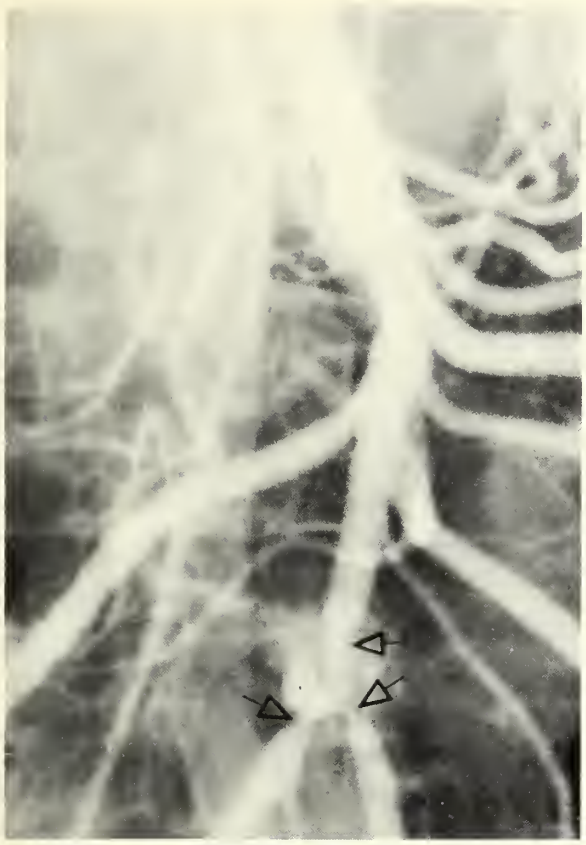

Figure 1.—Superior mesenteric artery injection. Irregularity in the proximal portion of the superior mesenteric artery may represent arteriosclerosis. More distally, a discrete, lobulated aneurysm is opacified. Adjacent portion of the superior mesenteric artery and an ileal branch are narrowed in proximity to the aneurysm (arrows). Surrounding arterial narrowing, a sign of infection, suggests that this is a mycotic aneurysm.

tion but all vision was lost in that eye. Lumbar puncture and brain scan were negative.

The patient's temperature became normal and remained so for one week. However, fever returned [38°C (100.4°F) rectally], and cultures of blood once more grew S. marcescens. An aggressive search for a septic focus, including roentgenograms of chest and bones and radioisotope scans of brain, lung, liver, and spleen, was unsuccessful. An intravenous pyelogram showed no focal defects. The left eye was enucleated, but it was not infected. Three weeks after admission, blood cultures remained positive for Serratia marcescens, which now showed stepwise resistance to the antibiotics used. Therefore, chloramphenicol (500 mg intramuscularly every four hours) was added to the regimen.

Because of the failure to demonstrate by less invasive methods a focus of infection seeding the circulating blood, multiple selective visceral arteriograms were performed, Aortic, iliac, carotid, vertebral, renal, and inferior mesenteric angiograms were normal, as was an inferior cavagram. A selective celiac angiogram, however, showed pooling of contrast medium in the liver, and selective study of the superior mesenteric artery demonstrated radiographic signs consistent with a mycotic aneurysm (Figures 1 and 2). Because there were no stigmata of endocarditis, cardiac murmurs, or septic pulmonary emboli, cardiac catheterization was not done.

Neither resection nor drainage of the hepatic abscess was performed because the surgical approach to its precise location was felt to carry too great a risk. Since only surgical removal of both foci could contribute to eradication of the infection, it was decided not to attempt resection of the mycotic aneurysm, but rather to treat the patient medically. Fortunately, he became afebrile and cultures of the blood became sterile. Gentamicin was discontinued on the 59th hospital day and carbenicillin and chloramphenicol were stopped on the 66th day. The patient remained afebrile, with sterile blood cultures, and was doing well several months after discharge.

Discussion

This case presents some unusual complications of bacteremia secondary to intravenous drug abuse. First, S. marcescens bacteremia without endocarditis is rarely seen in patients who abuse drugs, although endocarditis requiring surgical debridement has been reported in this setting.[2-4] Second, metastatic bacterial endophthalmitis as a complication of addiction has not been noted in the literature, although fungal endophthalmitis has been reported.[5] Third, the development of stepwise resistance to antibiotics in this strain of S. marcescens was a curious, worrisome observation. Finally, mycotic aneurysm and hepatic abscess, rarely seen in association with Serratia,[6,7] were sources of persistent bacterial showering into the blood stream, and this accounted for continued bacteremia despite aggressive antibiotic therapy.

After failure to locate the foci of infection by all noninvasive techniques, only laparotomy and angiography were available. Angiography was carried out and the sources of seeding were delineated thereby. Although simple aortography may be the best initial approach, this technique may not demonstrate an abscess or mycotic aneurysm since suboptimal opacification and superim-

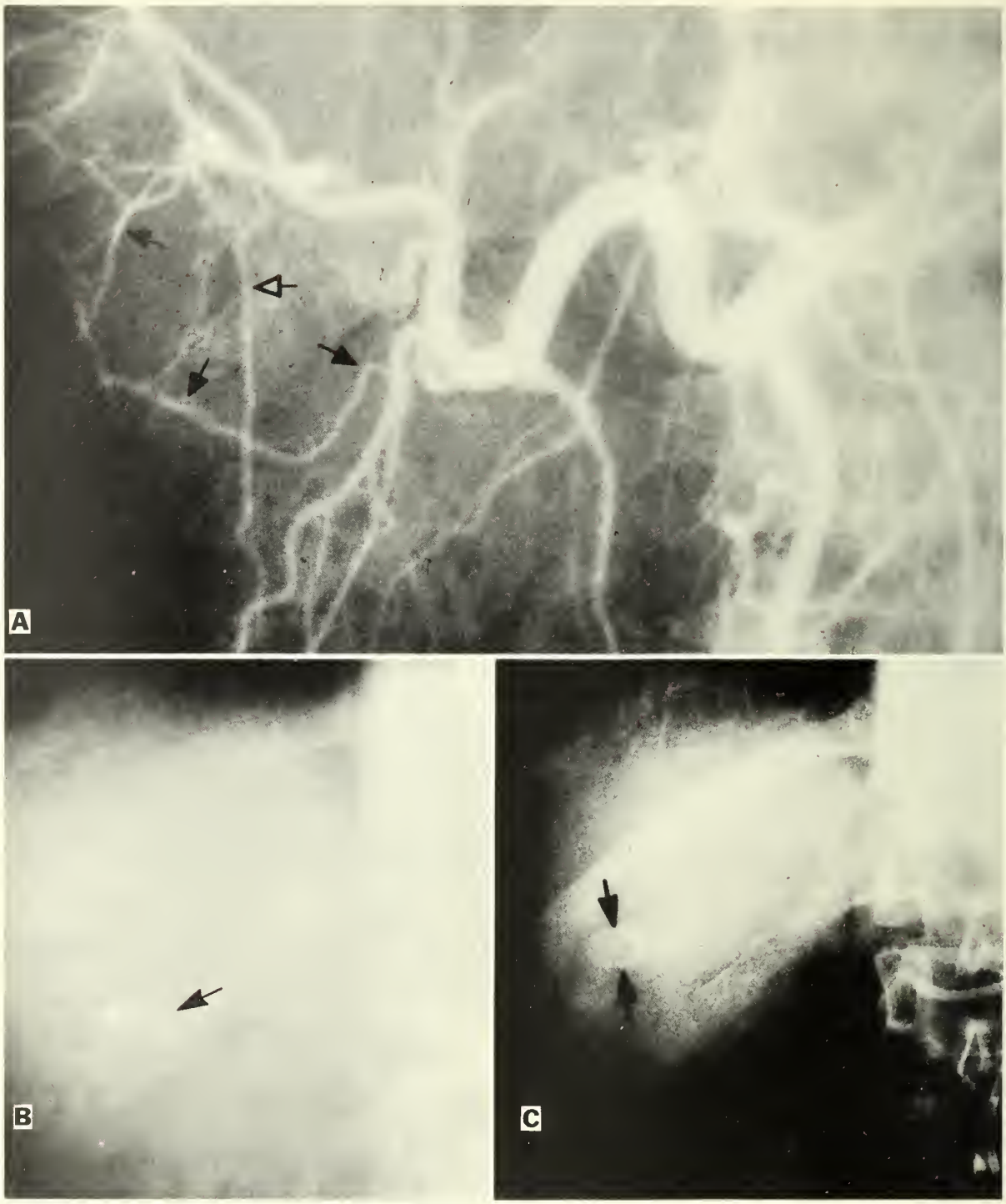

Figure 2.—Common hepatic artery injection. **A.** Several vessels in midportion of the right lobe of the liver are arched and displaced around a 5-cm lesion (solid arrows). The mass is avascular except for a single artery (open arrow), which is straightened. It courses through or is superimposed on the lesion. **B.** In the parenchymal phase, an ovoid collection of contrast medium appears at the center of the mass. A slowly filling branch of the hepatic artery (arrow) communicates with the extravascular collection of contrast medium. **C.** Ten minutes after the common hepatic artery injection, persistent vague opacification of the extravascular collection is seen (arrows). The mass appears 3 mm larger than in the parenchymal phase, indicating that extravasation has occurred into a liquid through which the contrast medium can diffuse further toward the periphery. This strongly suggests an intrahepatic abscess, rather than mycotic aneurysm, in the liver.

position of branch vessels reduce the diagnostic accuracy of the procedure (Figure 3). Therefore, selective angiography should be undertaken, beginning with the heart (when endocarditis is suspected) and abdominal viscera, because these organs are most likely to house the source of bacteremia. A mycotic aneurysm has many typical features (Figure 1); an abscess may be diagnosed by the particular vascular pattern it produces by displacement of vessels, by communication of an opacified vessel with a necrotic center, by defects in the parenchymal phase of the injection, or even by a hypervascular rim around the perimeter of the abscess (Figure 2). Injection of contrast medium into the celiac artery and, if possible, into the inferior phrenic artery allows a search for subphrenic, subhepatic, or peripancreatic abscesses. An inferior venacavagram is also useful, as mycotic aneurysms have occurred in this vessel. Examination of the extremities is more readily accomplished through clinical, thermographic, and ultrasonic methods. The more recent use of gallium scans may also prove useful in such clinical situations.

Surgical resection is the treatment of choice if all aneurysms that are sources of bacteria can be eradicated. Therefore, preoperative "total body" angiography is indicated. Surgical operation was contraindicated in our patient because of the unfavorable location of the hepatic abscess. It was surprising and gratifying that the foci of infection were rendered sterile by long-term antibiotic therapy alone.

The morbidity of such extensive angiography is low,[8,9] and such as does occur is probably related to the catheterization time and total volume of contrast medium infused. Therefore, this procedure should be undertaken in two or three stages, on separate days and preferably when the patient is clinically stable.

Our experience with this patient, who had unusual complications of illicit intravenous injection of a drug, points out that angiography can be a highly effective, relatively benign method of locating foci of infection after less invasive techniques have failed. While surgical resection is the treatment of choice, occasionally these foci can be eradicated by antibiotic therapy alone when operation is contraindicated.

Figure 3.—Abdominal aortogram. Although all major branches of the aorta are opacified, neither the aneurysm in the mesenteric artery nor the hepatic abscess is opacified.

Summary

Bacteremia caused by Serratia marcescens developed in a patient who was injecting pulverized methylphenidate hydrochloride (Ritalin®). Metastatic endophthalmitis, mycotic aneurysm, and hepatic abscess developed as complications of the infection. After initially successful treatment, recurrent bacteremia heralded the presence of occult foci of infection. "Total body" selective angiography then located these foci after other diagnostic techniques had failed.

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LETTERS *to the Editor*

Ophthalmia in the Newborn

To the Editor: Current morbidity reports from the State Department of Health show 81,646 cases of gonorrhea thus far in 1974. During this same period there were reported only 10 cases of acute newborn (gonorrheal) ophthalmia. This is a most curious discrepancy. Perhaps these latter are not being faithfully reported although they most certainly should be.

Is ophthalmia prevented by conscientious application of silver nitrate to the eyes? Regarding this I am most cynical. It is difficult to get the eyes open and introduce Crede's drops especially in the second eye. Particularly in the population where vaginal infection is so common, it is most unlikely this prophylaxis is carried out and even if it is, prevention is far from absolute.

I would hope, but hardly believe, detection of infection in the mother before delivery might be responsible, for this is certainly the most effective method of prophylaxis.

What is the explanation—and if it is failure of reporting, please confess.

Edward B. Shaw, MD
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Professor of Pediatrics, Emeritus

The "Executive" Physical Examination

To the Editor: In line with the current concern for what constitutes good medical practice, the so-called executive physical examination deserves to be re-evaluated. This if only because it has been considered to be "the best that money could buy."

The place of periodic physical examinations in ongoing health care is at best uncertain. I would propose that the benefits are even less certain when periodic examinations are performed outside the context of ongoing medical care. Unfortunately, this is common practice with executive physical examinations.

Executives often are referred to offices or clinics that specialize in doing only physical examinations. Or they may be examined by practicing physicians or clinics who will not provide ongoing care for the executive as a patient. In both such situations reports usually are furnished to the treating physician. These may arrive unexpectedly in the office mail.

I would submit that this practice—the physical examination performed by strangers—is an anachronism. The widespread availability of quality medical care and laboratory facilities makes this not only unnecessary but undesirable.

It is not good medical practice for a patient to be examined here and treated there. Yet a conflict of interest is often created when companies offer free examinations at company-designated facilities. At times the examination may even be within a company medical department, leaving the outside clinician with responsibility for the care of the patient and frequently without even a report of what has been found.

Executives are often intimidated into agreeing to any one of these arrangements. Not only is there a financial question, but there is reluctance to oppose the corporate will. The result can be confusing. A treating physician is reluctant to rely solely on the findings of others. Similarily, he is reluctant to duplicate work at the patient's expense. Medical care becomes fragmented.

Most pernicious of all is the uncertainty about the obligation for follow-up when an unsolicited report of an executive physical examination arrives in the office of the executive's ostensible physician. Is he obligated to read it? Is he obligated to request the patient to come in for a follow-up of abnormal findings? Or should he wait for the patient to call the office first? It is difficult to know what to do under such circumstances. Moral and legal issues are raised, without any easy answers.

Moreover, the isolated examination may even discourage the executive from making personal contact with a physician who has a responsibility to him for ongoing care. Normal examination findings may be interpreted as sufficient. Thus, when an emergency arrives, the executive may find himself with either a treating physician who barely knows him or at the mercy of whatever emergency services are available to doctorless patients.

I would suggest that executive physical exami-

nations be considered as an integral part of ongoing medical care. They should be performed by the executive's treating physician whenever possible. Should that physician not be able or willing to perform the comprehensive examination that is desired, he may suggest the use of another physician whom he normally uses as a consultant. That physician (or group) can later serve as consultant in the event of emergency or serious illness.

Finally, the utility of organizations that specialize only in doing physical examinations is to be seriously questioned.

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Asbestos Exposure and Cancer of the Larynx

TO THE EDITOR: Drs. Rom and Palmer, in their otherwise comprehensive review of asbestos-related diseases (Rom WN, Palmer PES: The spectrum of asbestos-related diseases. West J Med 121:10-21, Jul 1974), only briefly refer to the emerging evidence for an association between asbestos exposure and cancer of the larynx. We feel that this possible association deserves wide recognition in view of the difficulty of any one center accumulating sufficient cases for pathologic study.

A retrospective study of 100 male British patients with squamous carcinoma of the larynx presenting to the Liverpool Ear, Nose and Throat Hospital revealed a highly significant correlation with an occupational history of exposure to asbestos compared to age-matched control hospital inpatients with nonmalignant disease (31 percent versus 3 percent). A higher percentage of patients with laryngeal carcinoma smoked but among these the smoking histories were comparable in affected patients both with and without a significant exposure history. The mean latency period was noted to be 30 years between the first known exposure and frank clinical carcinoma, with a mean duration of exposure of 27 years.[1] A prospective study of 4,000 factory workers with presumed exposure has demonstrated two cases after 41 years, compared to an incidence in the general population of 1/50,000. One of the two had only one month of severe exposure.[2]

Separating an association with asbestos from possible association with smoking and alcoholism may prove to be a formidable problem. A recent epidemiologic investigation of pulmonary and laryngeal carcinoma has made reference to the problem of separating the effects of ambient particulate asbestos and other constituents of air pollution.[3] Other cancers of the head and neck may also be associated with asbestos exposure as suggested by similar preliminary data from the Liverpool group.[4]

Such a problem would lend itself to a search for asbestos bodies and other high atomic number particulates in surgical or necropsy tissue. The techniques of scanning electron microscopy and x-ray spectroscopic analysis have been recently applied in such cases.[5,6] These and other sophisticated techniques of visualization and analysis are now available for application by suitably equipped laboratories.

Examination of a few selected cases of laryngeal carcinoma having an accurate and complete occupational history of exposure to asbestos could yield data of practical and theoretical interest.

Application of advanced techniques such as these may contribute substantially to our understanding of the pathophysiology of environmentally induced disease.[7]

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Trauma Rounds

Chief Discussant
EDWIN G. BOVILL, MD

Editors
DONALD D. TRUNKEY, MD
F. WILLIAM BLAISDELL, MD

This is one of a series of Conferences on Trauma at San Francisco General Hospital

Refer to: Bovill EG: Orthopedic emergencies (Trauma Rounds). West J Med 122:76-79, Jan 1975

Orthopedic Emergencies

CLARK BOREN, MD:* The patient, a 27-year-old woman, was struck by a car and crushed as she walked around the rear of another vehicle. She was brought immediately to Mission Emergency Hospital. On physical examination the patient was seen to be in compensated shock characterized by tachycardia, hypotension and mild agitation. There were no obvious head injuries. However, a cerebral arteriogram made several hours later showed frontal lobe contusion. The chest was clear to auscultation and the abdomen was soft with no guarding. On examination of the lower extremities, compound fractures of both femurs and of both lower extremities including the tibia and fibia were noted. There was a severe degloving injury involving both upper legs to the knees. The skin from the legs was rolled up onto the lower abdomen, which was also partially involved in the degloving injury. There were palpable pedal pulses on the left but no pulses on the right. Capillary filling of the right foot was good.

Resuscitation was carried out with the appropriate placement of large bore catheters and the administration of two liters of Ringer's lactate. On exploratory laparotomy, done four hours after admission, no significant intraperitoneal injuries were noted. The fractures were managed by bilateral intramedullary rods to the femur and short leg casts. The extensive degloving injury was debrided, defatted and replaced as a full-thickness skin graft over the injury.

The patient's intraoperative course was very stormy, with extensive bleeding from all wounds and fracture sites. At one point there was no palpable blood pressure, necessitating reopening of the abdomen and clamping the abdominal aorta. Fluid replacement during operation consisted of 20 units of whole blood, 6 liters of colloid and 3 of crystalloid solution.

Since the initial operation, five subsequent operations for management of the lower extremity fractures have been required, consisting for the most part of realignment and placement of tibial pins. In addition, multiple skin grafting over the degloving injuries was necessary, particularly on the thigh. At present, however, the patient's wounds are 95 percent covered. Depressed sensorium due to the frontal lobe contusion was treated with dexamethasone (Decadron®) and there has been a complete recovery neurologically.

DONALD D. TRUNKEY, MD;† *I have two questions in regard to the course of this patient. First, was there a pelvic fracture in addition to the other injuries and second, were there any pulmonary complications?*

DR. BOREN: Yes, there was a type III pelvic fracture[1] involving the left pubic ramis. In regard to pulmonary function, the patient did remarkably

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well and there were no overt signs of the respiratory distress syndrome.

DR. TRUNKEY: Treatment of this patient represents a triumph in regard to resuscitation but more importantly, it was a triumph from an orthopedic standpoint. The management was optimal, in that the lesion was potentially fatal. We have asked Dr. Edwin Bovill to give his concepts of care in the type of case that has been presented today.

EDWIN G. BOVILL, MD:* I would preface my remarks by stating that usually orthopedic injuries are not life threatening. However, there are four situations where the management of a traumatized patient's orthopedic problems assumes a higher priority when accompanying many of the usually more urgent general surgical problems. These include in particular, fractures or dislocations of the spine, compound fractures, fractures associated with vascular compromise and fracture dislocations.

It behooves the emergency physician to be aware of the possibility of a spine fracture and to protect the patient to prevent any, or further, neurological damage. In particular the emergency-room physician must recognize that in multiply injured patients there may be many other more dramatic symptoms and signs than those accompanying a complete or partial spinal cord injury, and that every traumatized patient should have a sufficient preliminary gross neurologic survey to detect such a possibility. Unconscious patients, in particular, represent a clinical situation where paraplegia or quadriplegia or perhaps evidence of partial spinal cord injury can easily be overlooked since the lack of movement of the extremities is attributed to a more central lesion rather than to spinal eord involvement. Flaccid paralysis and the absence of withdrawal from pain stimuli are hallmarks suggesting acute spinal cord injury in comatose patients.

Open fractures or dislocations require meticulous debridement and irrigation of the wound, frequently followed by subsequent secondary closure or grafting to cover the wound. Although compound fractures are not of themselves life-threatening, in the emergency situation the incidence of residual infection with ultimate chronic osteomyelitis and possible loss of limb increases as the time increases between injury and debridement. Optimally, a compound fracture should be treated within six to eight hours of injury, since contamination usually remains superficial up to this point. From this time on, progressive bacterial invasion of the soft tissues takes place and local treatment may not be as effective in removing contamination.

The third area that requires urgent definitive treatment is the fracture associated with vascular impairment due either to a large artery laceration or compartmental vascular compression. The initial evaluation of the fractures should include a careful evaluation of the circulatory status of the limb. A warm extremity with good pulses is reassurance that vascular compromise is negligible. On the other extreme, a cool pulseless extremity, without sensation or with impaired muscle function is a nonviable limb. A cool limb with impaired pulses but intact sensation is a marginal limb. If reduction of the fracture does not result in immediate improvement of circulation, arteriographic studies are indicated and can usually be done on the operating table without the need to resort to special equipment.

Arterial repair should be made for any injury detected—preferably within four to six hours of injury to avoid the development of ischemic damage, muscle swelling and secondary vascular compression due to the development of one of the compartmental compression syndromes. Immediate decompression of the compartmental syndrome, unaccompanied by major artery injury, by fasciotomy can salvage muscle compartments or limbs. However, this must be begun early if it is to be of significant benefit. It is particularly important that following repair of a major arterial injury, skeletal fixation be achieved when possible to protect the arterial repair from reinjury from adjacent fracture fragments.

Another injury that requires immediate treatment is joint dislocation. The most important areas are the hip and knee. It is well documented that leaving a hip dislocated for periods longer than six to eight hours is associated with a high incidence of avascular necrosis of the femoral head with residual permanent disability.

Most dislocations in the extremities are readily apparent to the emergency-room physician and are relatively easy to reduce. The knee presents somewhat of a special problem since it has a higher incidence of major vascular damage and associated potential loss of limb due to the close relationships of the popliteal vessels to the dislocated parts. We

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consider it good judgment to do arteriographic studies in all knee dislocations as part of the initial assessment. Repair of any vascular injury detected assumes priority in the patient's management.

The last area that I wish to call your attention to is particularly poignant in regards to this patient. This is the treatment of fractures associated with severe soft tissue injury. In this patient, there not only was massive soft tissue injury but also multiple associated injuries. This puts the patient at risk for fat embolism or the disseminated intravascular clotting syndrome. This syndrome results from a combination of extensive soft tissue injury and shock.

Internal fixation helped to reduce the likelihood of further soft tissue injury. In addition, it permitted early mobilization, which is so essential in these patients to prevent the pulmonary complications so frequently seen following multiple injuries of this severity. In this patient, bilateral intramedullary rods were placed, making it much easier for the nurse to move the patient and obtain optimal ventilation of all lung segments.

The full-thickness skin loss involving all of both thighs in this particular patient created bilateral circumferential massive soft tissue wounds, interlaced with varying degrees of crush injury to the musculature. This could only have been managed in traction with any semblance of efficiency by placing the hips at 90 degrees and confining the patient to bed with little attention to fracture position. The internal fixation of this patient afforded stable fixation, not only for the femoral fracture, but also "splinted" the soft parts with the associated benefit in the later attempts to secure skin cover.

I would now like to turn the discussion over to Dr. Kevin Harrington, who was the orthopedic surgeon in charge of this patient.

KEVIN HARRINGTON, MD:* My comments will be confined to the management of this patient. The case represents the classic dilemma that the orthopedic surgeon is faced with in regard to immediate management. Although abdominal problems and cerebral problems in this patient were managed quickly, there still was a problem of volume loss due to continued loss of blood into the soft tissues around the fracture sites. In addition, I thought that the continuous soft tissue blood loss was aggravated by the flail nature of the fractures. This in itself was an indication for internal fixation. Certainly nonoperative management would have led to necrosis of the flaps and infection.

Another comment I would make about the management of this patient was the need for especially meticulous debridement and hemostasis for treatment of the soft tissue injuries. I think that this is another very important adjunct in preventing infection and further blood loss, and minimizing the amount of postoperative pulmonary complications. The degloving injury most certainly would have become necrotic and infected, and sloughed had it not been treated by immediate operation.

The other reason, which has already been mentioned, for internal fixation was to avoid the need for some type of skeletal traction which would have created a difficult nursing problem and made respiratory care difficult. A good argument could be made that the additional time required to place the intramedullary rods in this patient might have been detrimental. If the patient had died during the hypotensive episode, I am sure the orthopedic department could have been criticized. On the other hand, if we had not proceeded with placing intramedullary bilateral rods, I am sure that an equally strong criticism could be made if the patient had died in the postoperative period from complications which could be related to the immobilization required to treat the fractures. Even if the pulmonary complications had not developed, I am sure that one or both limbs would have been lost secondary to infection. It is because of these two opposing options that this patient presented a difficult clinical judgment problem at the time of initial management. Some orthopedic surgeons would be very critical of placing intramedullary rods. Our experience, at this hospital, is supported by that of Gregory at Parkland Hospital. Extensive injuries of this type are optimally managed by internal fixation. This ultimately will result in less mortality and morbidity despite the increased initial risk.

DR. TRUNKEY: *Dr. Blaisdell, would you have been critical of the decision to proceed with the extensive orthopedic procedures done in this unstabile patient?*

F. WILLIAM BLAISDELL, MD:† I find myself agreeing completely with Drs. Bovill and Harrington.

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The only alternative treatment available for these injuries was traction. This would have resulted in complete immobilization of this patient in a supine position. Respiratory complications would have been inevitable. Atelectasis, fat embolism, respiratory distress syndrome of trauma and pulmonary embolism are all hazards that this patient was subject to. These are preventable, at least in part by early mobilization.

The avulsion injury was another major problem and debridement was necessary to salvage skin coverage and prevent infection. Septic complications introduce an entirely new threat and major wound complication and in themselves are associated with a high incidence of respiratory failure. Operative treatment was the key to management in this case. In my opinion there is no such thing as a patient injured too badly to tolerate surgical operation. If a patient's injuries are so extensive as to be considered critical, operative treatment is mandatory to control blood loss, correct life-endangering problems and reverse the critical trend.

DR. TRUNKEY: *Dr. Bovill, I would like to ask you a question about the amount of blood which can be sequestered in a long bone fracture, such as one involving the femur. Would you comment on that please?*

DR. BOVILL: In a closed femur fracture alone, 1,000 to 2,000 ml of blood can be sequestered. A conservative estimate in this case would be that 2,000 ml of blood was lost from each of the open femur fractures, another 1,000 ml from each of the lower leg fractures and an indeterminate amount—at least another 1,000 ml—from the pelvic fractures. Since the patient's blood volume was not much over 5 liters, the potential volume loss from these injuries, if untreated, was sufficient to cause fatality. The orthopedic surgeon all too often underestimates the volume loss generated by "simple" fractures. Failure to initiate prompt volume resuscitation results in prolonged hypovolemia and all the secondary hazards such as respiratory failure. We monitor these patients carefully and use as the end point of resuscitation, good urine output and good peripheral perfusion as shown by warm, pink extremities.

DR. TRUNKEY: Dr. Bovill, the points you have made today should be helpful to all of us. I would like to emphasize your point that there are four categories of true orthopedic emergencies: (1) fractures or dislocations of the spine, (2) compound fractures, (3) fracture dislocations and (4) fractures associated with vascular compromise. All of these require prompt evaluation and treatment—optimally, within six to eight hours of injury.

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Special Article

Refer to: Andrus LH, Fenley M: Assistants to primary physicians in California. West J Med 122:80-86, Jan 1975

Assistants to Primary Physicians in California

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The mid-level practitioner movement is no longer experimental; nurse practitioners and physician's assistants in California have proved to fill a necessary and viable professional role in the delivery of primary health care. The physician's assistant law (AB2109) and the Experimental Manpower Act (AB1503) have facilitated the training and functioning of these new health care professionals; more comprehensive laws are still needed to permit optimal utilization. National agencies for approval of teaching programs and testing of individual graduates will play an increasing role in the accreditation and certification procedures. Professional role difficulties, issues of sex and questions of delegation of responsibility are being resolved and it is hoped that a more equitable and patient-oriented system is evolving.

ANY SURVEY of health care in California or in this nation shows that we are still plagued by a deficit in primary health care.[1-3] The mid-level practitioner movement is essentially the explosive response to this need.[4,5]

Deficit of Primary Physicians

The lack of health care is easily visible in the poorer states, yet even in wealthy California, in spite of our eight growing medical schools (the University of California's five and three private ones) and in spite of the influx of physicians into California from elsewhere (two thirds of California's physicians come from outside California), the deficit is still major.[6-8]

Part of the problem is a maldistribution of specialties. Surveys using "ideal" physician to population ratios in Northern California[9] and the entire state[10] show that there is a general geographic deficit of primary care physicians and surplus of some specialties such as general surgeons. Whether it is a rural area, such as Glenn County with its one physician to every 2,200 people, or a large city, like San Francisco with one doctor to every 204 people,[10] all sectors of the population, and particularly the lower economic groups, suffer from an unavailability of sufficient numbers of primary health care professionals.[11-13]

This shortage has its historical beginnings in the Flexner report of 1910[14] which scorned the preceptor method of medical education and which, inspired by the explosion of medical knowledge, encouraged increased specialization among physicians. The military's World War II deferment policies for residents in specialty training and preferential ranking of drafted specialists furthered

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the drift from primary care practice. Progressive tightening of hospital privileges also made the general practitioner a second class citizen. These factors precipitously decreased the numbers of primary care physicians.

A Change of Emphasis to Primary Care

Fortunately, over the last ten years there has been an awakening to the need to provide more comprehensive health care to greater numbers of people.[15-18] The American Board of Family Practice, incorporated in 1969, finally established a specialty in primary care, and today 203 approved family practice residencies are training some 2,500 residents across the United States and turning away many applicants.[19] These programs continue to grow in numbers and respectability.

Mid-Level Practitioners, Part of the Answer

Even with more physicians, however, it has become obvious that the delivery of primary care solely by physicians is inappropriate. First, overburdened primary care doctors often have needed help as they find themselves buried in episodic care. Furthermore, many patient needs such as health education, health maintenance, diagnosis and therapy of common diseases and the whole gamut of socioeconomic factors can be just as expertly handled by nonphysicians whose educations focus on these areas.[4] Thus the mid-level practitioner movement has grown in order to supply these auxiliary and supplementary health care professionals.[20-25]

Within this group of mid-level practitioners, two general names have emerged in California: the nurse practitioner and the physician's assistant. We feel the distinction between the two is arbitrary and the political more than functional. As the California Nurses' Association explains, the physician's assistant may be said to extend the medical services provided by the physician, while the nurse practitioner provides, in addition, a different and complementary dimension to the care process based on prior background in nursing.[26] Physicians express different preferences which we feel are more often emotional than rational.

The breadth and depth of capabilities and responsibilities of these mid-level practitioners bridge that traditional gap between physicians on the one hand and registered nurses, licensed vocational nurses and health aides on the other.

This is not new ground, of course. For centuries there have been people who functioned in this area. In Russia, feldshers date back to the 15th century and have had established schools for over 100 years.[27] Busy physicians have always worked with nurses and office assistants who, formally trained or not, performed tasks that by law should have been done only by an MD. The mid-level practitioner movement, then, in addition to being a response to society's needs, is an effort to legitimize these mid-level responsibilities through the establishment of educational curricula, certification and back-up legislation.

The UCD Family Nurse Practitioner Program

The Family Nurse Practitioner Program in the Department of Family Practice at the University of California, Davis, is one of the pioneering programs in the nation in the development and preparation of nurse practitioners. It began in 1969 as a Master in Public Health program for baccalaureate degree nurses, initially at the School of Public Health in Berkeley. After one year of operation, the program moved to the Davis campus.

It is an 18-month program which includes one year of didactic instruction and clinical practice, followed by a six-month internship. The curriculum consists of specified units in medical history taking; physical examination; pathophysiology; diagnosis and treatment of common problems; clinical management of selected, stable, chronic diseases and preventive medicine. Each student must demonstrate understanding of the subject matter and competence of clinical skills in these units to be certified.

Students are selected for the program so as to include nurses most apt to practice in areas of need. Primary care providers in rural areas, particularly family physicians, are asked to identify candidates for the program. Original requirements as to the type of registered nurse (RN) degree received—whether diploma, Associate in Arts (AA) or Bachelor of Science (BS)—have been dropped. Students with baccalaureate degrees may pursue a master's degree through extra course work, and non-baccalaureate nurses receive university credit which may be applied to a bachelor's degree.

While the program primarily trains students from California and southern Oregon, some selected students are being trained to become the core faculty for similar programs in other states. Presently we have two black nurses in training for a rural program in Tuskeegee, Alabama.

In order not to interrupt the delivery of care

in the areas from which these (California) candidates are selected, the program has developed a work and learn teaching program in which, with University direction, community physicians teach the students. One day a week the students travel by car or chartered plane to the Davis campus for intensive didactic instruction by the full-time University faculty. Their physician preceptors, all members of the clinical faculty of the Department of Family Practice at Davis, supervise their acquisition of clinical skills while working with them in their private offices the rest of the week.

The program is currently involved in further decentralization of the educational program into rural areas through the development of satellite training sites, strategically located in medical centers in rural areas. The first such program is in Santa Rosa, where nine nurses from coastal rural areas of California visit for their once-a-week lectures rather than going to Davis. Their professors are physicians and nurse practitioners who live and work in Santa Rosa. The curriculum is the same as that delivered in Davis.

The work and learn method in decentralized areas is an attempt to guarantee better distribution of skilled health care professionals, improve primary health care in rural areas, and increase the relevancy of the curricular material. In addition it provides excellent experimental models of health care systems which are being studied. For example, we have analyzed the comparative academic success of nurses with varying educational backgrounds and found no significant difference between baccalaureate and non-baccalaureate RNs in the grades they received. It appears that motivation and on-the-job training are much more important than academic degree in determining how well the student does in class.

Are Mid-Level Practitioners Legal Now?

The history of establishing the legal status of nurse practitioners and other physician extenders in California has been a rather slow and tortuous process with much debate over territorial rights.[28] In California, as elsewhere, the Board of Medical Examiners administrates the activities of the practice of medicine, and the Board of Nursing Education and Nurse Registration regulates nursing activities. These mid-level practitioners, bridging the gap between the two professions, do not clearly come under either group's jurisdiction, although legislation is underway to establish the authority.

Physician's Assistant Legislation

For the non-RN mid-level practitioner, the physician's assistant law (AB2109, Duffy), which was passed in 1970, established the regulatory authority as the California State Board of Medical Examiners. It covers physician's assistants and medex, who are graduates of a two-year college program and generally not RNs, although many have military corpsman backgrounds. The legislation sets the precedent for limiting the numbers of such assistants to two per physician and requires that the physician be approved as a supervisor.

Physician's assistants are limited in the scope of tasks permitted; for example, pelvic and endoscopic examinations are prohibited. The law requires that the physician be present with the physician's assistant under most circumstances. There are five training programs for physician's assistants in California, three of them in primary care (at Stanford, at the Charles Drew Center in Watts of the University of California at Los Angeles and at the University of Southern California).

Experimental Manpower Legislation

Legislation covering mid-level practitioners with RN degrees has been even slower to emerge, possibly because the RN was already a licensed health care professional. In 1972, AB1503 (Duffy), now Chapter 1350 of the California Health and Safety Code, established a mechanism for the approval of allied health personnel training programs under the Experimental Manpower Act. Most nurse practitioner programs in California are now operating under this law. Our program at Davis was the first to be approved under this act, and since then some 33 programs throughout California have been accepted.[29] As of December 1973, there were 120 graduates or prospective graduates of family nurse practitioner programs in California.[30]

The statute establishes the legality of a physician's delegating tasks to a nurse practitioner trainee, as long as the physician is "immediately available for consultation either personally or through electronic means." This permission to include the telephone or two-way radio allows the nurse practitioner much greater geographic independence than the physician's assistant has. It is a more permissive law in that it provides for greater breadth of function.

Modification of the Nurse Practice Act

A bill amending the Nurse Practice Act of 1939 (AB3124, Duffy) was signed into law in June

1974. It gives clear authority for those functions and procedures which have had common acceptance and usage, as well as setting the stage for the expanded medical role of the RN. AB2879 (Duffy), which also has been signed by the governor, includes more precise definitions of "common acceptance." Yet neither bill specifically recognizes the nurse practitioner, nor do they cover the more specialized roles of the highly trained family nurse practitioner, pediatric nurse practitioner, adult nurse practitioner, obstetric-gynecologic nurse practitioner and psychiatric-mental health nurse practitioner.[30]

Nurse Practitioner Legislation

AB3187, another bill introduced by Assemblyman Duffy (February 1974), was the most definitive attempt to date to formalize the identity of the nurse practitioner. It proposed the establishment of a Council of Nurse Practitioners under the Department of Consumer Affairs, rather than under either the nursing or medical boards of the state. It provided for curriculum requirements and accreditation of training programs, licensure of nurse practitioners who were RNs or licensed vocational nurses (LVN) graduated from these training programs, and disciplinary proceedings. Membership of the council was to be seven members. One RN, one LVN, one MD, one RN who was director of a nurse practitioner program, one RN with advanced clinical training, one MD on a medical school faculty and one public member.

Unfortunately, AB3187 was defeated. Territorial disputes threatened it since its conception. The California Nurses' Association formally testified against this bill in March before the Assembly Health Committee[31] on the grounds that it would have given authority over nursing practice to an independent regulatory agency. Proponents of the bill argued that the separate council it proposed would have been a more representative group. We agreed with this stand because we believed the council would have provided a prototype for future health science boards of examiners with much-needed broad representation of various kinds of providers as well as consumers.

While some people feel that the expansion of the Nurse Practice Act under AB3124 is sufficient, we feel there is still great urgency for legislation which will regulate standardized, competency-based educational programs and licensure and certification specifically for mid-level practitioners.

From various points of view, some legislation is desperately needed. To the consumer of health services, laws are essential to guarantee the public that these mid-level practitioners have specific skills and knowledge, as well as to encourage the production of these much needed primary health care providers. For the physician, legislation granting certain authority to the mid-level practitioner will permit the delegation of many time-consuming tasks and the extension of new health care services. And for the mid-level practitioner who is presently in training or who enters such a program in the future, the certification is needed to afford formal recognition of training, capabilities and financial worth.

National Standards for Mid-Level Practitioners

The National Board of Medical Examiners now has an examination for assistants to the primary physician which will undoubtedly play an increasingly important role in the training and certification of these professionals. Physicians who pass National Board examinations find this acceptable in almost every state in lieu of board examinations for state licensure,[32] and many medical schools use the national examination instead of their own finals or as an additional requirement for graduation. All states recognize national specialty board testing. This trend, if applied to nurse practitioners, will certainly simplify the process and permit greater mobility of professionals.

In December 1973, the National Board of Medical Examiners conducted the first such certifying examination for assistants to the primary physician. Of the 880 candidates who took the test, 68 percent received their training in physician's assistant programs and 9 percent in nurse practitioner programs. The mean standard score was 494 points, the standard deviation 84. The minimum score for passing was 400; 85.5 percent passed. Fourteen graduates of our Family Nurse Practitioner Program took the examination; they all passed, with a mean standard score of 536.[33]

The analysis of test scores by the Board showed (as did our own experience with baccalaureate and non-baccalaureate nurses) that educational background is not the essential ingredient. No significant differences in scores were found among examinees trained in physician's assistant, medex and nurse practitioner programs. Those with clinical experience acquired after graduation, however, scored higher than those without this experience.

The Board saw this result as evidence of the relevance of the examination, since it appeared to measure knowledge and skills actually used and improved in the clinical environment.[33]

Who Certifies Programs Nationally?

The only national standards for mid-level practitioner programs are those adopted by the American Medical Association's House of Delegates in late 1971, and set out in *The Essentials of an Approved Educational Program for the Assistant to the Primary Care Physician.*[34] This was the collaborative effort of the American Academy of Family Physicians, the American Academy of Pediatrics, the American College of Physicians and the American Society of International Medicine, all of which sponsor the Joint Review Committee on Educational Programs for the Assistant to the Primary Care Physician. The Committee evaluates applications for accreditation, and the American Medical Association's Council on Medical Education, upon the Committee's recommendations, accredits programs.[35] The Council on Medical Education was recognized in February 1974 by the United States Office of Education as the national accrediting agency for these programs.

In March, the Council on Medical Education approved our Davis program, actually the first and, to date, the only nurse practitioner program to be approved by this group. The only other program in California that has received the Council's approval is the medex program of the Charles Drew Postgraduate Medical School, University of California at Los Angeles. As of June 1974, a total of 43 programs for assistants to the primary care physician had been approved nationally.

Acceptance of Mid-Level Practitioners

Patient acceptance of nurse practitioners and physician's assistants has been so favorable that it is no longer an issue; various studies show that when the role of the mid-level practitioner is properly introduced to the patient there is uniform acceptance.[36,37] Furthermore, their contribution to improved and more comprehensive health care is well established.[38]

The major deterrent to wider use of the mid-level practitioner has been the lack of acceptance by physicians.[39] Often doctors in greatest need of help and in areas of greatest care deficit are the ones most threatened by the formally trained mid-level practitioner. Fortunately, as the usefulness and competence of these professions become more widely known, physician acceptance is following. We have been impressed by our own preceptors' overwhelming enthusiasm for their mid-level colleagues once they have had a chance to work with them.

Changing Roles

Physicians have traditionally been selected for being self-reliant, competitive individuals, not for their ability to work cooperatively with others, especially others with less formal education. Their medical school training has always encouraged their authoritarian qualities. Yet today, as all our institutions are doing, medicine is undergong change.

The historical authority of the physician, due to his education and legal responsibility, is breaking down because of various factors. Health care providers are organizing; health care is thought of more and more as a public right; payment systems are beginning to emphasize payment for total care rather than for specific physician services. In short, health care is becoming less provider oriented and more consumer oriented.

Realistically, in office relations the physician is still the employer, the boss in the sense of legal and medical responsibility. This dominance is particularly evident in the physician's reluctance to delegate tasks.[40] The nurse, traditionally taught to take orders, frequently finds it difficult to take the aggressive role needed to made decisions.[16] On the other hand, there is a trend in the nursing profession to seek freedom from physician dominance and to demand more independent status.[41]

Battle of the Sexes

Role conflicts are exaggerated by traditional male and female images: the *male* doctor, physician's assistant and medex; the *female* nurse and nurse practitioner.[41] It is true that at present women are restricted to defined roles within the health care delivery system.[42] Yet we have had experience working with men and women filling all ranges of professional roles; we have found that the roles are inevitably determined much more by the setting in which they work than by sex or prejudicial images. We have men and women in our Family Nurse Practitioner Program, and women are joining the traditionally male medex programs in increasing numbers. There is an obvious trend in medical schools to accept more women. Fortunately the stereotypes are breaking down as sex lines are crossed. When roles are finally de-

fined by patient oriented functions, rather than traditional professional images, many of these problems will be resolved.

Dependence, Independence and Interdependence

The degree of dependence or independence of the mid-level practitioner with respect to the physician is a balance between legal limitations and capabilities. Ideally it is determined by the specific competencies of the persons involved.

In practice, mid-level practitioners have proved to be competent and capable of handling many patient problems alone, within the prescribed protocols worked out by the physician. Our Family Nurse Practitioner graduates reported that in 70 percent of patient visits, they were the only professional the patient saw.[43] All patient contact activities were under the general supervision of the physician, of course, and most patients seen on a continuing basis or with complications also saw the physician. Others have also reported on the increasing ability of mid-level practitioners to extend physician services in a fairly independent manner.[40,43]

What we see as the ideal is the physician and mid-level practitioner as colleagues who work together as members of a larger primary health care team.[25,44,45] Our plea is for greater *interdependence* of all members of the team.

Communication and Supervision

An essential for safe and effective utilization of the nurse practitioner, as well as for good office relations, is satisfactory communication between the mid-level practitioner and the physician. Delegation of tasks, whether directly or through protocols and consultation, should include sufficient supervision to assure that the nurse practitioner collects pertinent data, accurately interprets the data and recognizes deviations from the normal and understands his or her limitations in diagnosis and therapy.[30]

How Are Mid-Level Practitioners Paid?

Most mid-level practitioners are paid a straight salary by a physician or institution. Few data are available on the size of salaries in California, but a limited survey done in the summer of 1974 showed that in 19 private practices in Northeastern California the mean annual salary received by mid-level practitioners was $12,390; four reported salaries below $12,000, and the maximum was $18,000.[46] A national study by Scheffler and Stinson showed a mean of $9,869 and a range of $4,599 to $21,362; women physician's assistants at that time started at salaries averaging $2,200 less than men physician's assistants, and after two years' experience the gap widened to a difference of $4,550.[47] An American Medical Association study of 1973 salaries across the nation showed a mean annual rate of $11,560 and a range of $7,200 to $22,500; however, there was still an average difference of $2,040 between salaries of men and women physician's assistants.[48] We may conclude that although sex discrimination in salaries is disappearing slowly, the upward trend of salaries in general signifies increasing recognition of the utility of mid-level practitioners.

Some physicians have worked out salaries for various allied health workers as a percentage of volume or by profit-sharing arrangements based on the team's or the individual member's performance. A few physicians share risks of loss and profit with all the professionals in the office.

Unfortunately, to date the performance of mid-level practitioners, like that of physicians, has usually been gauged by traditional fee-for-service financing, under which preventive medical measures are either not included or poorly remunerated. One of the greatest challenges facing the health care system is the development of financial incentive systems that reward quality of care and emphasize preventive medicine and patient education.

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Special Article

The Saga of Osteopathy in California

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On March 19, 1974 (in the case of D'Amico, et al versus the Board of Medical Examiners, et al) the California Supreme Court removed restrictions enacted in 1962 against the licensing of new osteopathic physicians and surgeons in California. The court ruled, in effect, to reestablish the licensing of DO's in California under the jurisdiction of the long-dormant State Board of Osteopathic Examiners. By its ruling, the state Supreme Court opened yet another chapter in the continuing saga of osteopathy's relationship to medicine in the delivery of health care to Californians.

The story begins with Andrew Taylor Still, MD, an ex-Civil War Army surgeon and itinerant physician who, in 1874, first propounded the principles of osteopathic medicine.[1] Still likened the human body to a machine and theorized that all disease was caused by structural deviations in the vertebrae. He and his early followers maintained that these dislocations of the vertebrae adversely affected the nervous system which, in turn, acted to impair the necessary circulation of the blood and other body fluids.

Early osteopathic treatment therefore consisted chiefly of the manipulations of the spine. According to these founding fathers of osteopathy, surgical operation was sometimes a necessary treatment but drugs and vaccines, herbs and simples, not only did no good, they often induced illness. Given some of the bogus medications often in use at that time, there was some justification for the early osteopaths' suspicion of chemotherapy.

Dr. Still practiced as an itinerant physician for more than 20 years before deciding to open a school which would train young men and women to become osteopathic physicians. The first school chartered to offer instruction in osteopathic medicine was opened in Kirksville, Missouri. Its first faculty consisted of Andrew Still himself, and one or two of his followers. By 1910, there were twelve osteopathic schools throughout the country, of which three were in California. Only one California osteopathic school was to survive, the Los Angeles School of Osteopathy—later called the College of Osteopathic Physicians and Surgeons. It enrolled its first students in 1901 and subsequently matured to the point where it won recognition as perhaps the best of the American osteopathic schools.

The Osteopathic Association of the State of California was incorporated under the laws of California on December 29, 1900. In 1917, the name was changed to the California Osteopathic Association (COA). COA's chief objectives were to establish at California's osteopathic schools educational standards and an educational curriculum which would be considered comparable to that offered at accredited medical schools.

Even as far back as 1901, California osteopaths fought for the same unlimited practice privileges as then enjoyed by the medical profession. The California legislature yielded to these demands partially by passing a law which permitted osteopaths to be awarded an "Osteopathic Physician's Certificate" administered by a licensing board composed of members of the osteopathic profession. This was a limited license, however, and osteopaths were not permitted to prescribe drugs or perform major surgical operations.

In 1907, the first comprehensive California Medical Practice Act was passed. The Act repealed the previous medical and osteopathic act, and provided for a composite medical board to

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regulate all systems of practice. From 1907 to 1919, osteopathic physicians and surgeons had to pass the same examination for licensure as allopathic medical graduates. Then, in 1919, the board refused to examine any more osteopaths. Though this action was overruled in court, the court's verdict did not deprive the board of its power to impose future restrictive rules and regulations which could have the net effect of limiting the practice of osteopathy in the state.

To insure their professional survival, the COA developed in 1922 an initiative act creating a separate board of examiners. The American Osteopathic Association (AOA), indicating that the development of such an initiative should be the national organization's responsibility, opposed the initiative. The California Medical Association also opposed the initiative because it was believed that a separate board would further fragment medical practice in the state. Despite this combined opposition, the Osteopathic Initiative Act was passed by the electorate in 1922.

With its own Board of Examiners now firmly written into law, osteopathy in California became an equal and distinct medical profession. Osteopaths owned their own college, their educational standards were improving and they were permitted to prescribe drugs and perform major surgical procedures.[1] And to assure equality at law, the 1922 Osteopathic Act incorporated into itself both the Medical Practice Act and all amendments that might be made to it in the future.

A distinction must be made between the type of medicine practiced by osteopaths in 1930 and that of their historical antecedents of 1900. By the 1930's, California DO's no longer considered manipulation of the vertebrae a cure-all. Lewis Reed, in a comprehensive and scholarly study of osteopathy published in 1933,[2] noted this change in the osteopathic art. "Osteopathy," he said, "instead of being the theory of the cause of all diseases, is tending to become the theory of *one* cause of some diseases." Reed further pointed out that "it is difficult to define present-day osteopathy in a way that will distinguish it as a theory of healing distinct from 'regular' medicine." As osteopathy grew as a profession, young osteopaths appeared as eager to use drugs, radiation and surgical operations as their Doctor of Medicine counterparts. The manipulative osteopath in California was being gradually superseded.

Because of osteopathy's increased professional stature, its heightened professional and educational standards, and its common acceptance of the tenets and techniques of the medical profession, as early as 1938 a few of its practitioners felt the time was ripe to attempt to merge their school, the College of Osteopathic Physicians and Surgeons, with the University of Southern California Medical School. Exploratory talks between COA and the California Medical Association did take place but many MD's opposed the idea at that time and the merger never materialized.

Throughout the ensuing decade or so, as the two medical professions continued to draw closer together in practice and philosophy, the interest in merging the two professions gathered more and more support from DO's and MD's alike. In 1955, Dr. John Cline, a San Francisco surgeon, former CMA and American Medical Association president and chairman of AMA's Committee on Osteopathy, presented the results of his committee's survey of osteopathic colleges in the United States to the AMA House of Delegates. The committee noted that, within the framework of the AMA's Principles of Medical Ethics, the teaching in these schools did not fall into the "cultist" category. It also established that students in osteopathic schools received a fairly adequate training in the clinical and basic sciences. What they chiefly lacked, the Cline Committee reported, was an opportunity for postgraduate clinical training and a closer overall relationship with the medical profession.

Though the interest in a merger between the two professions grew in California, the American Osteopathic Association continued its adamant opposition to the idea, arguing that osteopathy should retain its status as a separate but equal medical profession. Yet the facts in California belied this position. Equal opportunities were at no time available to California DO's. Their hospital facilities, except for the osteopathic wing of the Los Angeles County General Hospital, were poor. Because their osteopathic school was always in need of money, its quality of teaching and its ability to support research tended to suffer. For California osteopaths, merger with the medical profession would bring them from the periphery of the medical community into the medical mainstream.

By 1960, it became apparent that COA and CMA were very close to reaching merger agreement. In July of that year, the American Osteopathic Association formally instructed the COA to cease merger negotiations with CMA. Three months later,

at its House of Delegates meeting, the COA voted to ignore the national body's resolution and to continue negotiations with CMA. The AOA almost immediately withdrew support for COA and recognized as its California representative the Osteopathic Physicians and Surgeons of California, a splinter group of COA members who opposed the proposed merger.

The merger came to fruition in May 1961, when the CMA House of Delegates voted 296 to 63 in favor of ratification of the merger agreement with COA. For the medical profession, the merger was a culmination of nearly 20 years' negotiations to unify the medical community. Under the merger agreement, DO's holding valid physician and surgeons' licenses in the state of California would be able, if they chose, to change to MD's. The College of Osteopathic Physicians and Surgeons in Los Angeles would become the California College of Medicine, an accredited medical school affiliated with the Association of American Medical Colleges. The CMA would work to absorb DO's within the structure of existing county medical societies, but until they were so absorbed, a special, statewide Forty First Medical Society would be created.

The final step to professional unification was the passage of Proposition 22 in 1962. Approved by an overwhelming majority of Californians, Proposition 22 stripped the Board of Osteopathic Examiners of all powers to issue new licenses and limited its activity to the regulation of those osteopaths already licensed. Of the 2,250 practicing DO's in California, all but 400 became MD's.

The unification in 1961 and 1962 standardized the education, examination, licensure and degree for the practice of medicine within the state. Medical postgraduate courses offered at all medical schools were made available to members of the Forty First Medical Society. For the first time residency programs in the specialties of neurosurgery, plastic surgery and psychiatry were opened to the former DO's.

Assimilation of former DO's into the educational programs and the organizational activities of organized medicine continued throughout the period between 1962 and 1974. Several bills were introduced into the state legislature to negate Proposition 22 and to provide reciprocity licensure for out-of-state DO's but these bills were soundly defeated. Then, in March 1974, in a lawsuit brought by eight graduates of out-of-state osteopathic colleges (the D'Amico case), the state Supreme Court ruled that denying them licenses to practice medicine in California violated the equal protection provisions of both state and federal constitutions. While the Court's ruling does not affect those DO's who converted to MD status as licentiates of the Board of Medical Examiners subsequent to 1962, it does reestablish the licensing of DO's in California, including reciprocity for those qualified DO graduates licensed by other states.

California now finds itself in a unique position, with two medical licensing boards—the Board of Medical Examiners and the Board of Osteopathic Examiners—administering a single medical practice act. As of October 15, 1974, the California Board of Osteopathic Examiners had received 2,964 inquiries for applications from DO's outside the state. As of that date, also, the Board had awarded 340 new DO licenses. These figures are likely to continue to rise rapidly in the months ahead.

The conditions which enabled the merger to take place in 1962 have changed significantly. Today, there are no schools or colleges of osteopathy, no osteopathic house staff training programs and no osteopathic hospitals in California—all of which existed before 1962. Yet the one condition that enabled the two professions to join in good conscience—the undisputed overlap and blurring of distinctions in the training and practice of both professions—is even more in evidence today than in the past. It is on this basis that CMA and other groups are continuing to work to bring future and present California DO's into the mainstream of California medicine.

A recent American Medical Association report cites the dramatic improvement in facilities and faculties of osteopathic schools. The report states that "the current competition for admissions to medical schools has been reflected in osteopathic schools and permits the presumption that students of increasing ability are entering osteopathic schools." It further notes that the "Educational Standards of Colleges of Osteopathic Medicine," as approved by the Board of Trustees of the AOA, now contains requirements similar to those developed by the AMA for allopathic medical schools.

In an independent nationwide survey, the National Disease and Therapeutic Index (NDTI) recently found a close parallel between osteopathic and allopathic medical practices. The NDTI report found the two professions treated similar patients and disease conditions and used similar methods of treatment.

Currently, there are nine osteopathic colleges nationwide, educating approximately 3,000 future DO's. By 1978, it is estimated that over 1,000 DO's a year will be graduated. While most physicians trained in osteopathic medicine are general practitioners, there are also DO specialists in general surgery, obstetrics, ophthalmology, psychiatry and many other specialties.

Since 1969, the AMA has admitted qualified DO's to full active membership. Twenty-four state medical societies now accept qualified osteopaths as active members. In the 1972-73 academic year, 417 DO's were enrolled in various AMA-approved residency training programs and 128 osteopathic physicians held AMA-approved internships. Osteopathic physicians also participate in postgraduate medical education programs offered by the AMA and state medical associations. In addition, 14 specialty boards have opened their examinations to qualified osteopathic physicians, and residencies in those specialties are open to qualified graduates of osteopathic colleges.

Currently, the American Hospital Association and the Joint Commission on Accreditation of Hospitals require that MD's and DO's meet identical requirements for appointments to hospitals' medical staffs and hospital privileges.

The California Medical Association, representing its 26,000 physician members, continues to support the principle of a unified medical profession for California. Bridging this principle with the recent Supreme Court ruling, CMA's Council has recommended acceptance for membership in CMA and its component medical societies of qualified DO's practicing in California.[3] The CMA, through its Committee on Osteopathy, has been in close contact with the California Hospital Association, the Deans of California medical schools, and many others, in order to formulate suitable policy and regulations to assure that DO's are accorded the same protection of due process and the same opportunities and privileges on professional staffs of hospitals that are granted to doctors of medicine. The CMA Council's recommendations, designed to allow equal opportunities for CMA membership to qualified DO's, will be considered by the CMA House of Delegates at its 1975 meeting in February. These recommendations reflect a desire on the part of organized medicine to ensure to the public a uniformly high standard of medical care by all physicians, whether they be DO's or MD's.

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Medical Information

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Tumor Associated Antigens

Clinical Implications

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THE DIAGNOSIS AND MANAGEMENT of patients with cancer may be aided nowadays by determining the minute levels of certain products secreted by the neoplasms into the body fluids.

The antigenic materials may be hormones or enzymes, or they may be classified as "tumor associated antigens," which are substances of unknown biological function that may evoke specific antibodies in experimental animals.

The synthesis of this wide range of tumor-associated substances is commonly attributed to genetic derepression. Genes normally dormant in the adult are thought to be activated in the corresponding malignant cells. However, since some of the tumor products are normally detectable in low concentrations, the distinction might be quantitative rather than qualitative.

The interpretation of levels of tumor-associated antigens in blood or urine requires consideration of a number of factors which include the rate of synthesis of the antigen by the tumor itself and the metabolic and excretory processes, so that any factors which interfere with these mechanisms may influence the levels detected. For example, if the antigen is degraded in the liver, hepatotoxic drug therapy might produce elevated antigen levels, unrelated to the status of the neoplasm.

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The laboratory methods for the detection of such antigens fall generally into two categories, radioimmunoassays, the most sensitive, and immunodiffusion and counterelectrophoresis, which are only moderately sensitive. In either case, these methods could be applied to cancer screening, or diagnosis, or tumor localization, or monitoring the course of the disease.

The only tumor for which there is a reliable screening test is the choriocarcinoma. Radioimmunoassays for human chorionic gonadotropin (HCG) make it possible to detect almost all the tumors at a time when they are curable. Although this is a rare tumor, such a screening program is now carried out on a national scale in the United Kingdom.[1]

Localization of the tumors is theoretically possible if one can add a radioactive label to the appropriate antibody. This has been demonstrated in experimental animals as the isotopically labelled antibody concentrates in the tumor-bearing areas.[2]

Monitoring the course of the disease seems to be one of the better established applications for diagnostic means of this kind. Currently radioimmunoassay for HCG and now carcinoembryonic antigen (CEA) and alpha fetoprotein (AFP) are used for monitoring the course of the disease in a variety of malignant neoplasms.[3,4]

Characteristics of Some Tumor-Associated Antigens

Alpha Fetoprotein (AFP)

Alpha fetoprotein is a serum protein characteristic of the fetus which was identified in adult mice with transplantable hepatoma and in patients with primary liver cell carcinoma by the Russian investigators, Abelev and Tatarinov, in 1963 and 1964. These proteins have the electrical mobility of an alpha globulin, are normally undetectable in the adults but increase in values late in pregnancy. Much higher than normal values are found in the presence of anencephalic fetuses and spina bifida. Transient increases in serum levels have also been recorded in severe cases of serum hepatitis, and in such instances the elevations seem to precede clinical improvement.

The prevalence of elevated serum levels in patients with hepatic cell carcinoma, as determined by immunodiffusion, has varied from about 80 percent in Uganda and Indonesia to about 40 percent in the United States. The use of counterelectrophoresis, in which an electrical field forces the antigen and the antibody against each other, has

resulted in increased sensitivity of this test.[5] AFP usually is present in about 1 microgram per milliliter of serum. It is also elevated in 25 percent of adult patients and 75 percent of children with teratocarcinoma. Serum AFP determinations are valuable in detecting, diagnosing, and following the results of therapy in patients with primary liver cell carcinoma.

Carcinoembryonic Antigen (CEA)

Gold and Freedman, in Montreal in 1965,[6] demonstrated that rabbits immunized with extracts of human colonic cancer produced antibodies to the tumor. Similar antigens were found in the fetal gastrointestinal tract in early pregnancy and therefore they called this protein carcinoembryonic antigen (CEA). This is a beta globulin present both in metastatic and primary lesions. Large metastatic lesions are the best source of the antigen with a yield of about 10 mg per kilogram of tumor.

Different methods of radioimmunoassay for CEA have been proposed. The one currently approved by the Federal Drug Administration involves perchloric acid extraction of the CEA in a radioimmunoassay which ends by precipitation of the antigen antibody complex with a special gel. Alternate methods have been described in which a double antibody is used, and the range of normal values has varied with the different types of test.

Extensive evaluation has indicated that CEA assays are not a reliable means of detecting early carcinomas of the colon and rectum. Positive results have occurred only with large localized tumors and with the presence of metastasis. The CEA test, however, provides a means of monitoring the course of the disease and for detecting relapse earlier than would otherwise be possible.[7] It is now generally felt that elevated values are found in association with a wide range of carcinomas, primarily colorectal and pancreatic. Lower abnormal levels even in the absence of malignant disease have been reported in cirrhosis, ulcerative colitis, pancreatitis, Crohn's disease, in heavy smokers and the aged.

CEA activity has been found in the urine of 85 percent of patients with urothelial tumors. In our experience values of 40 nanograms per milliliter of plasma have almost always been associated with malignant disease.

The detection of tumor-associated antigens in serum or plasma by either counterelectrophoresis, immunodiffusion or radioimmunoassay now has a firmly established place in the diagnosis and management of a limited range of malignant disorders. However, it is evident that much wider range of malignant lesions produce substances that can be detected by immunological techniques, and so this field of clinical research is very likely to expand. In looking for tumor-associated antigens, it might be necessary in the future to perform a battery of tests. Tumor localization techniques look promising from available animal experiments where the antibody against CEA has been labelled with short-lived isotopes which have been observed to localize in areas of known metastatic disease. The current tests do have limitations, however, as in the case of the CEA and the AFP. Neither can be recommended alone for use in screening for cancer, nor can either be regarded as an absolute test for malignant disease. When these limitations are kept in mind, however, we find that at present we have several new kinds of information which we did not have two years ago and which will undoubtedly help toward better management of patients with malignant neoplasms.

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Medical Information

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Constipation and Laxative Abuse

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"A good reliable set of bowels is worth more to a man than any quantity of brains."[1]
—HENRY WHEELER SHAW

ELIMINATION OF DIETARY WASTE is a fundamental process in man. Learned behavior, with regard to bowel function, begins early in child development, and by adulthood one has acquired his bowel habit or elimination pattern. This is based not only on physiologic mechanisms within the gastrointestinal tract, but also "the time of day, the nature of the preceding meal, a particular toilet, and often a cigarette or other added factor . . . "[2]

There is no obvious public consensus as to what constitutes a normal bowel pattern. Thus, prompted by early experiences with toilet training, later advice from friends, and a constant barrage of advertising from the communications media, many adults feel their elimination process is somehow not normal, and thereby become "constipated." A wide variety of subjective symptoms are then ascribed to constipation, and with the easy availability of proprietary cathartics, one begins the slide to laxative abuse.

The amount of money expended for laxatives in this country has been estimated at 200 million dollars annually.[3] Thirty to 50 different drugs that aid defecation are available to the interested buyer in Palo Alto drug stores (personal survey). Lader found that 30 percent of women and 40 percent of men surveyed from a greater London population were self-medicating with laxatives.[4] In another study, 3 percent of those studied who were not and 14 percent of those who were in hospital took laxatives more than once a week.[5]

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Normal Physiology

The amount and nature of fecal material depends on physiologic mechanisms within the gut. This has been extensively reviewed in various texts[2,6] and need not be covered here. Suffice it to say that after absorption and propulsion of food have occurred in the small bowel, the resulting residue is presented to the colon where further absorption of water and electrolytes takes place. Waste material is moved toward the rectum by several types of propulsive or motor activity involving single or multiple segments of the colon.[7] Net forward movement approximates 5 cm per hour, and after meals this may increase to 10 cm an hour.

As the rectum fills and becomes distended, the defecation reflex is set off, and the desire to defecate occurs. The internal anal sphincter (smooth muscle) relaxes, abdominal and chest wall muscles contract, intra-abdominal pressure increases, and the rectum is evacuated. The external anal sphincter (striated muscle) is under voluntary control, and normally in a contracted state. If one desires to defecate, the external sphincter relaxes; however, the act may also be voluntarily inhibited, and the external sphincter remains contracted, pressure in the rectum decreases and stool is returned to the descending colon.[2,6]

Constipation

Definitions of constipation vary. Almy describes it as the passage of stools that are either excessively dry, infrequent, or of insufficient size.[2] Heffernan refers mainly to hard stools.[8] Patients seem to pick one or all of these characteristics in describing what they mean by "constipation."

One might then ask what constitutes a normal bowel pattern. Connell et al,[5] after interviewing over 1,500 Londoners of all ages, found 99 percent to have from three movements a day to three a week. Healthy male prisoners were noted to have considerable variability in the time between evacuations, the average interval being about 27 hours.[9]

Various methods have been used in defining the physiologic abnormalities present in "constipated" patients. Motility studies of the colon, using balloon catheters,[10] have shown less pressure activity

in the upper rectum of constipated than in normal persons. Recordings in the sigmoid area revealed longer activity time intervals in constipated persons under the age of 40. Waller et al[11] found that persons with constipation had little or no increase in pressure waves during meals. Wangel and Deller[12] noted one constipated patient to have a pressure gradient directed away from the anal canal, in contrast to those with diarrhea. Hinton and Lennard-Jones[13] measured gut transit time, using radiopaque insoluble pellets. Normal subjects passed the first marker within 72 hours of swallowing it, and virtually all had been passed within five days. Constipated subjects took longer by both measurements. Using colonic perfusion techniques, Devroede and Soffie[3] also found delayed transit in patients with idiopathic constipation (defined as less than 3 stools per week).

Causes of Constipation

Successful treatment of a patient with constipation depends on careful identification of the cause (obstructing lesions, systemic disorders, drugs, environment, psychogenic). A thorough history and physical examination, appropriate laboratory tests, sigmoidoscopy, and barium examination of the bowel are usually required.

Following such studies, obstructing lesions such as cancer, diverticulitis, and inflammatory bowel disease are apparent and can be dealt with. British investigators[14,15] have expressed belief that obstinate constipation can be secondary to elongated or redundant segments of colon. Parks et al[16] have described "the syndrome of the descending perineum" as yet another anatomic cause of constipation. In these patients, after years of excessive abdominal straining the perineal and pelvic muscle tone is poor, with subsequent downward bulging of the rectal mucosa and a sensation of incomplete evacuation and "constipation." The diagnosis of Hirschsprung's disease, which previously depended on biopsy and radiologic findings, has been aided by anorectal manometric studies. By using rectal balloons, it has been shown that rectal distension causes relaxation of the internal anal sphincter in normal persons and contraction in patients with Hirschsprung's disease.[17,18]

Systemic disorders that lead to chronic illness and debility may cause hard or infrequent stools owing to prolonged bed rest, poor dietary habits and weak musculature.[19] Patients with endocrine disorders such as hypothyroidism[20] and hypercalcemia[21] may complain bitterly of constipation secondary to decreased motility.

TABLE 1.—*Laxatives*

Type	*Example*
1. Stimulants	Cascara, phenolphthalein, castor oil
2. Lubricants	Mineral oil, dioctyl sodium sulfosuccinate
3. Bulk formers	Methylcellulose, psyllium seed
4. Saline cathartics	Magnesium sulfate, milk of magnesia

Drugs such as anticholinergics, antacids, analgesics or sedatives may cause a sluggish bowel pattern.[22]

Environmental factors can be very important relative to usual bowel function. Travel, the changing of habits previously associated with defecation, admission to the hospital and so on can lead to extreme constipation. The patient should be aided in keeping his usual pattern no matter what the circumstances. In the hospital, privacy, avoidance of strict nursing routine, exercises, and the use of a toilet or bedside commode help to avoid hardness or irregularity of stools.[19]

In my experience, the commonest cause of constipation is psychogenic. Usually, the patient has developed poor bowel habits at an early age or has neglected the defecation reflex. Laxative abuse soon follows, and finally "nothing works." Treating such patients requires considerable patience and time. One must carefully explain normal colonic and anal physiology, the need to develop a set routine for bowel function, the importance of diet,[23] and above all, the need to avoid laxative or enema abuse. The patient must be allowed to discuss his own notions of "constipation" fully so that erroneous ideas can be logically dispelled. Other causes of constipation must be ruled out. Finally, as one is weaned from a pattern of laxative abuse, various regimens using enemas, suppositories, or bulk laxatives, or combinations of these measures, may be *temporarily* required.[2,8]

Laxatives

Before discussing the clinical features of laxative abuse, a brief classification of the various laxatives should be remembered (Table 1). Detailed descriptions of the pharmacology of each type can be found in various reviews.[24-27]

In brief, the stimulants basically increase motor activity of the small or large bowel, or of both. Phillips et al,[28] using rabbit ileal loops, have shown

TABLE 2.—*Clinical Features of Laxative Abuse*

1. Factitious diarrhea	3. Osteomalacia
2. Electrolyte imbalance	4. Protein losing enteropathy
hypokalemia	5. Steatorrhea
hypocalcemia	6. Cathartic colon
hypermagnesemia	7. Liver disease

that the irritant laxatives may also work by inhibiting active sodium transport from lumen to plasma and thus lead to an osmotic cathartic effect. Laxatives of the lubricant class soften the stool and thereby promote easier evacuation. Bulk formers, by increasing residue and stool volume, stimulate bowel motility and may have an additional lubricating effect. Saline cathartics, because of poor absorption, exert an osmotic effect in the gut lumen. The resulting increased volume of water promotes intestinal motility.

Articles describing the use of cholic acid[29] and lactulose syrup[30] as laxatives have recently appeared, but the role of these agents is not yet clear.

Laxative Abuse

The chronic use of laxatives (Table 2) ultimately leads to increasing constipation and the need for even stronger purges. The need to reeducate chronic users has been discussed above. There remains, however, a much smaller group of patients who abuse laxatives to the point that serious illness ensues (Table 2). These patients may go to great lengths to hide their laxative ingestion,[30-33] despite numerous admissions to hospitals, serious symptoms and even surgical operation. Often they are subconsciously very hostile, and thus have guilt feelings which are alleviated by self punishment. Anger and confrontation tactics by the physician are of little benefit, and such patients desperately need psychiatric help.[31]

Patients with severe laxative abuse and diarrhea may present with serious electrolyte imbalance. Schwartz and Relman[34] first described this in 1953, reporting upon two female patients with hypokalemia secondary "to the overuse of laxatives." Since then, numerous other cases have been recognized and thoroughly investigated.[33-37] Fatigue, motor paralysis, cramps, and poor renal function are prominent symptoms. Low blood volume and loss of sodium in the diarrheal stools may also lead to secondary hyperaldosteronism.[33,37] Fletcher et al[38] described a patient with profound hypokalemia from the surreptitious ingestion of Ex-Lax.® At first she was believed to have Bartter's syndrome because of elevated plasma renin activity, increased aldosterone, and juxtaglomerular cell hyperplasia on renal biopsy. Profound hypocalcemia has been described both in adults[39,40] and infants[41,42] with overdoses of laxatives containing phosphate. In patients with chronic renal failure, laxatives containing magnesium may cause hypermagnesemia and clinical toxicity.[43]

Frame et al[43] reported the case of a 51-year-old woman with hypokalemia, hypocalcemia and osteomalacia after 20 years of phenolphthalein abuse. She improved after the drug was stopped. In 1968 investigators[45] at the National Institutes of Health described two patients with chronic diarrhea from laxative abuse. Both had undergone exploratory laparotomy. Clinical features were electrolyte depletion, poor renal function, steatorrhea, hypoproteinemia, and well documented protein losing enteropathy.

Another feature of the prolonged abuse of irritant cathartics may be the "cathartic colon."[46] Findings on barium study of the colon may mimic inflammatory bowel disease very closely. One may visualize constricted areas, loss of haustral markings and even changes in the terminal ileum. British pathologists have reported thickening of the muscularis mucosae, excessive submucosal fat[47] and damage to the myenteric plexus in the colonic specimens from such patients.[48]

It is now clear that the use of laxatives containing oxyphenisatin can lead to serious chronic liver disease.[49-54] The patients are indistinguishable from those with chronic active hepatitis and may have several immunologic abnormalities including a positive lupus erythematosus clot test, smooth muscle and antinuclear antibodies. When the laxative is stopped, most improve, although one death has been reported.[53]

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in memoriam

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CMA member physicians may register by sending a check for $30 (made payable to the California Medical Association) indicating the name of the program (conference or institute) to

CMA, Dept. of Medical Education
731 Market Street
San Francisco, CA 94103

A hotel reservation form and program will be sent upon receipt of your fee.

For additional information, you may call CMA, Dept. of Medical Education at (415) 777-2000, ext. 141.

Today's woman doesn't want to
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If adverse reactions such as spotting or breakthrough bleeding occur when she starts on an oral contraceptive, you're among the first to hear about it. Anxious, worried, she's in your office immediately. Or on the phone, at all hours.

Ovral® helps eliminate questions.

To help her maintain her busy schedule —and not interfere with yours—you might consider starting her on Ovral. Experience has shown that most patients who start on Ovral stay on Ovral. Its low incidence of spotting, breakthrough bleeding and other common adverse reactions undoubtedly contributes to this fine record.*

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"Normal" periods, few drop-outs.

You know how important a "normal" period is to a woman on an oral contraceptive. With Ovral, duration of cycle, length of period and amount of flow usually resemble those of normal periods. This is one reason why the drop-out rate for Ovral is low—4.5% in clinical trials totaling 127,872 cycles.

Today's woman tends to stay on Ovral. She's seldom in your office or on the phone with questions or complaints.

Ovral.® A very "quiet" pill.

*Serious as well as minor adverse reactions have been reported following the use of all oral contraceptives. The physician should remain alert to their earliest manifestations and in the event of serious adverse reactions should avoid any oral contraceptives. Special note, contraindications, warnings, precautions, and adverse reactions in the accompanying IN BRIEF should be carefully considered.

OVRAL®

Each tablet contains 0.5 mg. norgestrel with 0.05 mg. ethinyl estradiol.

Wyeth Laboratories
Philadelphia, Pa. 19101

Important information on next page.

Ovral.® A very "quiet" pill.

IN BRIEF.

SPECIAL NOTE: Oral contraceptives have been marketed in the United States since 1960. Reported pregnancy rates vary from product to product. The effectiveness of the sequential products appears to be somewhat lower than that of the combination products. Both types provide almost completely effective contraception.

An increased risk of thromboembolic disease associated with the use of hormonal contraceptives has now been shown in studies conducted in both Great Britain and the United States. Other risks, such as those of elevated blood pressure, liver disease and reduced tolerance to carbohydrates, have not been quantitated with precision.

Long-term administration of both natural and synthetic estrogens in subprimate animal species in multiples of the human dose increases the frequency for some animal carcinomas. These data cannot be transposed directly to man. The possible carcinogenicity due to the estrogens can neither be affirmed nor refuted at this time. Close clinical surveillance of all women taking oral contraceptives must be continued.

INDICATIONS: For oral contraception.

CONTRAINDICATIONS: 1. Thrombophlebitis, thromboembolic disorders, cerebral apoplexy, or a past history of these conditions; 2. Markedly impaired liver function; 3. Known or suspected carcinoma of the breast, 4. Known or suspected estrogen dependent neoplasia; 5. Undiagnosed abnormal genital bleeding

WARNINGS: 1. The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism, and retinal thrombosis). Should any of these occur or be suspected, the drug should be discontinued immediately.

Retrospective studies of morbidity and mortality in Great Britain and studies of morbidity in the United States have shown a statistically significant association between thrombophlebitis, pulmonary embolism, and cerebral thrombosis and embolism and the use of oral contraceptives. There have been three principal studies in Britain[1-3] leading to this conclusion, and one[4] in this country. The estimate of the relative risk of thromboembolism in the study by Vessey and Doll[3] was about sevenfold, while Sartwell and associates in the United States found a relative risk of 4.4, meaning that the users are several times as likely to undergo thromboembolic disease without evident cause as non-users. The American study also indicated that the risk did not persist after discontinuation of administration and that it was not enhanced by long continued administration. The American study was not designed to evaluate a difference between products. However, the study suggested that there might be an increased risk of thromboembolic disease in users of sequential products. This risk cannot be quantitated, and further studies to confirm this finding are desirable.

(1) Royal College of General Practitioners: Oral Contraception and Thromboembolic Disease. J. Coll. Gen. Pract. 13:267-279, 1967. (2) Inman, W.H.W. and Vessey, M.P. Investigation of Deaths from Pulmonary Coronary and Cerebral Thrombosis and Embolism in Women in Child-Bearing Age. Brit. Med. J. 2:193-199, 1968. (3) Vessey, M.P. and Doll, R. Investigation of Relation between Use of Oral Contraceptives and Thromboembolic Disease. A Further Report. Brit. Med. J. 2:651-657, 1969. (4) Sartwell, P.E., Masi, A.T., Arthes, F.G., Greene, G.R., and Smith, H.E. Thromboembolism and Oral Contraceptives: An Epidemiological Case-Control Study. Am. J. Epidem. 90:365-380 (Nov.) 1969

2. Discontinue medication pending examination if there is sudden, partial or complete loss of vision, or if there is sudden onset of proptosis, diplopia, or migraine. If examination reveals papilledema or retinal vascular lesions, medication should be withdrawn. 3. Since the safety of Ovral in pregnancy has not been demonstrated, it is recommended that for any patient who has missed two consecutive periods, pregnancy should be ruled out before continuing the contraceptive regimen. If the patient has not adhered to prescribed schedule the possibility of pregnancy should be considered at the time of the first missed period. 4. A small fraction of the hormonal agents in oral contraceptives has been identified in the milk of mothers receiving these drugs. The long range effect to the nursing infant cannot be determined at this time.

PRECAUTIONS: 1. The pretreatment and periodic physical examinations should include special reference to breasts and pelvic organs, including Papanicolaou smear since estrogens have been known to produce tumors, some of them malignant, in five species of subprimate animals. 2. Endocrine and possibly liver-function tests may be affected by treatment with Ovral. Therefore, if such tests are abnormal in a patient taking Ovral, it is recommended that they be repeated after the drug has been withdrawn for two months. 3. Under the influence of estrogen-progestogen preparations, preexisting uterine fibromyomata may increase in size. 4. Because these agents may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, cardiac or renal dysfunction, require careful observation. 5. In breakthrough bleeding, and in all cases of irregular bleeding per vaginam, nonfunctional causes should be borne in mind. In undiagnosed bleeding per voginam, adequate diagnostic measures are indicated. 6. Patients with a history of psychic depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree. 7. Any possible influence of prolonged Ovrol therapy on pituitory, ovarian, adrenal, hepatic or uterine function awaits further study. 8. A decrease in glucose tolerance has been observed in a significant percentage of patients on oral contraceptives. The mechanism of this decrease is obscure. For this reoson, diabetic patients should be carefully observed while receiving Ovral therapy. 9. The age of the patient constitutes no absolute limiting factor, although treatment with Ovral may mask the onset of the climacteric. 10. The pathologist should be advised of Ovrol therapy when relevant specimens are submitted. 11. Susceptible women may experience an increase in blood pressure following administration of contraceptive steroids.

ADVERSE REACTIONS OBSERVED IN PATIENTS RECEIVING ORAL CONTRACEPTIVES: A statistically significant association has been demonstrated between use of oral contraceptives ond the following serious adverse reactions: thrombophlebitis, pulmonary embolism, cerebral thrombosis.

Although availoble evidence is suggestive of an association, such a relationship has been neither confirmed nor refuted for the following serious adverse reactions: neuro-oculor lesions (e.g., retinal thrombosis ond optic neuritis).

The following adverse reactions are known to occur in patients receiving oral contraceptives: nausea, vomiting, gastrointestinal symptoms (e.g., abdominal cramps and bloating), breakthrough bleeding, spotting, change in menstrual flow, amenorrhea during and after treatment, dysmenorrhea, edema, chloasma or melasma, breast changes (tenderness, discomfort, enlargement and secretion), change in weight (increase or decrease), changes in cervical erosion and cervical secretions, suppression of lactation when given immediately post-partum, cholestatic jaundice, migraine, acne, rash (allergic), hypertension, rise in blood pressure in susceptible individuals, mental depression, pain in legs, arms or body, paresthesias, allergy, palpitations, vasomotor symptoms, dyspnea, insomnia, blurred vision, chest pain, urinary tract symptoms, dyspareunia, neuralgia and myalgia, excess salivation, dryness of mouth, heartburn, minor eye problems.

Although the following adverse reactions have been reported in users of oral contraceptives, an association has been neither confirmed nor refuted: anovulation post-treatment, premenstrual-like syndrome, changes in libido, changes in appetite, cystitis-like syndrome, headache, nervousness, dizziness, fatigue, backache, hirsutism, loss of scalp hair, erythema multiforme, erythema nodosum, hemorrhagic eruption, and itching and vaginal discharge.

The following laboratory results may be altered by the use of oral contraceptives—hepatic function: increased sulfobromophthalein retention and other tests; coagulation tests: increase in prothrombin, Factors VII, VIII, IX and X; thyroid function: increase in PBI and butanol-extractable protein-bound iodine and decrease in T_3 uptake values; metyrapone test, and pregnanediol determination.

Note: For more specific details on Ovral, refer to package insert.

Wyeth Laboratories Philadelphia, Pa.

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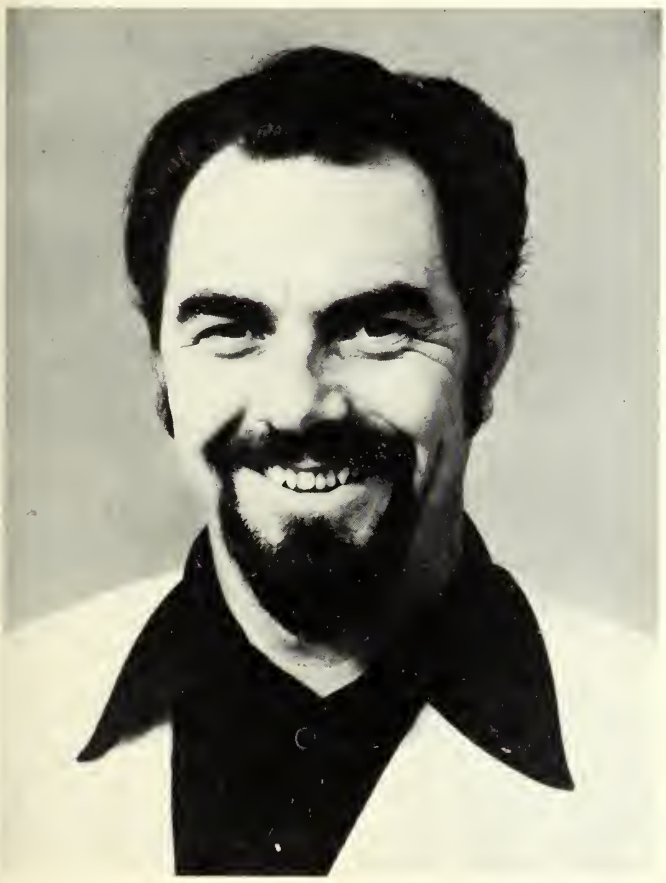

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SANTA BARBARA—Family Practice physician for full-time staff position at County-operated teaching hospital. Salary to $34,088 ($35,831 if Board Certified) plus fringes. CONTACT: Edgar Rosen, MD, Med. Dir., Santa Barbara General Hospital, P.O. Box 3650, Santa Barbara, CA 93105. Phone: (805) 967-2311.

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The department delivers health care services utilizing staff in the following specialities: medical services, community services, nutrition, family-planning, nursing, health education, social services, laboratory, alcohol and drug rehabilitation and diversion, and administrative services.

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Send résumés to **Director of Personnel, Room 100, 205 W. Broadway, Long Beach, California, 90802** by January 31, 1975.

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OPPORTUNITY FOR INTERNIST EDUCATOR-CLINICAN (must be Diplomate American Board of Internal Medicine) as training director, Internal Medicine Pathway in a Primary Care Residency Program. Applicant should have experience in the organization and administration of a teaching and patient care program in general internal medicine, including ambulatory care, on either a university campus or at a medical school-affiliated hospital. Interested individuals should write for a detailed job description and send their Curriculum Vitae to Robert H. Crede, MD, Chairman, Division of Ambulatory and Community Medicine, University of California, San Francisco, San Francisco, CA 94143. The University is an Equal Opportunity employer with an Affirmative Action Program.

ORTHOPEDIST: Board Certified or Board Eligible. 200-bed GM&S Hospital in San Francisco Bay Area. Salary to $36,000 depending on qualifications, supplemented by attractive benefits: Retirement, life and health insurance, liberal leave system; opportunity for medical school affiliation; provisions for paid continuing education programs. An equal opportunity employer. Contact Chief, Surgical Service, Veterans Administration Hospital, Livermore, CA 94550. (415) 447-2560.

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(Continued on Page 36)

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Your reservation request should include the definite date and hour of your arrival and departure.

All reservations, except for suites, must be made through The Biltmore Hotel, 515 South Olive Street, Los Angeles 90013 **by January 21, 1975.**

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1. Gertler, M. M., et al.: Geriatrics *25*:134-148 (May) 1970.

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(Continued from Page 32)

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San Juan Capistrano, Calif.

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DR. DAVID BARNES
400 Newport Center Dr., No. 208
Newport Beach, Calif. 92660

Or Call: **(714) 833-3145**

BOOKS RECEIVED

(Continued from Page 13)

PHYSIOLOGICAL OPTICS—Charles J. Campbell, MD, Med ScD, Professor of Clinical Ophthalmology, College of Physicians and Surgeons, Columbia University; Charles J. Koester, PhD, Applied Research Manager, American Optical Corporation, Framingham Centre, Massachusetts, Lecturer in Ophthalmology, College of Physicians and Surgeons, Columbia University; M. Catherine Rittler, DSc, Special Lecturer in Ophthalmology, College of Physicians and Surgeons, Columbia University; and Robert B. Tackaberry, BS, Director, Product Development, Scientific Instrument Division, American Optical Corporation, Buffalo, NY. Harper & Row, Publishers, Inc., Medical Department, 2350 Virginia Avenue, Hagerstown, MD (21740), 1974. 286 pages, $15.00.

REVIEW OF MEDICAL MICROBIOLOGY — Eleventh Edition — Ernest Jawetz, PhD, MD, Professor and Chairman, Department of Microbiology, Professor of Medicine, Lecturer in Pediatrics, University of California, San Francisco; Joseph L. Melnick, PhD, Professor of Virology and Epidemiology, Baylor University College of Medicine, Houston; and Edward A. Adelberg, PhD, Professor of Human Genetics, Yale University School of Medicine, New Haven. Lange Medical Publications, Drawer L, Los Altos, CA (94022), 1974. 528 pages, $8.50.

NOT MADE OF WOOD—A Psychiatrist Discovers His Own Profession—Jan Foudraine. Macmillan Publishing Co., Inc., 866 Third Avenue, New York City (10022), 1974. 414 pages, $9.95.

THE SECRET STRENGTH OF DEPRESSION—Frederic F. Flach, MD, Associate Clinical Professor of Psychiatry, Cornell University Medical College, Attending Psychiatrist, Payne Whitney Clinic of New York Hospital. J. B. Lippincott Company, 521 Fifth Avenue, New York City (10017), 1974. 288 pages, $7.95.

STRESS WITHOUT DISTRESS—Hans Selye, MD, Director of the Institute of Experimental Medicine and Surgery, University of Montreal. J. B. Lippincott Company, 521 Fifth Avenue, New York City (10017), 1974. 171 pages, $6.95.

SURGICAL TREATMENT OF HEAD AND NECK TUMORS—Edited by Jorge Fairbanks Barbosa, MD, Chief, Group of Surgery, Central Institute of the Associaçao Paulista de Combate ao Cancer, Corresponding Fellow of the Society of Head and Neck Surgeons and of the American Academy of Facial Plastic and Reconstructive Surgery. Grune & Stratton, Inc., 111 Fifth Avenue, New York City (10003), 1974. 311 pages, $35.00.

TREATMENT OF INBORN ERRORS OF METABOLISM—Current Treatment and Future Prospects—Proceedings of the Tenth Symposium of The Society for the Study of Inborn Errors of Metabolism—Edited by J. W. T. Seakins, R. A Saunders and C. Toothill. Longman Inc., 72 Fifth Avenue, New York City (10011), 1974. 260 pages, $21.50.

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painless injection instrument that uses ordinary disposable syringes

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Neoject is a patented instrument that totally eliminates the pain of routine IM injections. This instrument is easy and rapid to use, and will be appreciated by all your patients. Controlled application of anesthetic at the injection site makes injections 100% painless. The syringe and needle are not visible to the patient in use, reducing the apprehension many patients feel toward injections.

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Neoject uses standard 2.5 and 3cc disposable syringes, and may be used with any medication for IM injections. The instrument may be adjusted to administer any size dosage. Penetration depth is adjustable for 1/2 or 7/8 inch.

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Enclosed is A Check A Money Order for $_____

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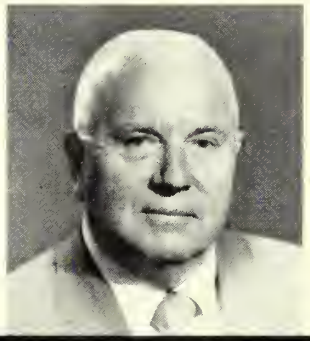
City_____ State_____ Zip_____

I've enclosed $_____ (Includes postage, handling & tax) Allow 2-3 weeks for delivery

The Role of the Detail Man

Opinion & Dialogue

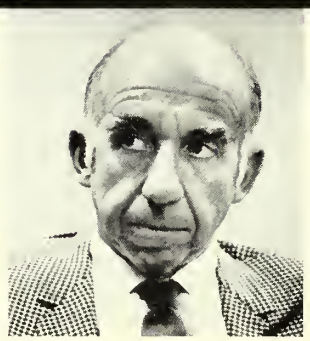


Dr. Willard Gobbell
Family Physician
Encino, California

"I may be prejudiced, but I am very much in favor of the detail men I meet. Most of them are knowledgeable about the drugs they promote and can be a great help in acquainting me with new medication."

Family Physician's Perception

I think that most general practitioners in this area feel as I do about the detail man. Over the years I have gotten to know most of the men who visit me regularly and they in turn have become aware of my particular interests and the nature of my practice. They, therefore, limit their discussion as much as possible to the areas of interest to me. Since I usually see the same representative again in future visits, it is in his best interest to supply me with the most honest, factual, as well as up-to-date information about his products.



Dr. Jeremiah Stamler
Chairman
Department of Community Health and Preventive Medicine, and Dingman Professor of Cardiology
Northwestern University Medical School

"In the total picture of dealing with health problems in this country, there is a potential for detail men to play a meaningful role."

The Positive Influence

My contact with representatives and salesmen of the pharmaceutical industry is the type of contact that people in a medical center, research people, and academic people have and that's in all likelihood on a somewhat different level from that of the practicing physician.

Let me touch on how I personally perceive the role of the sales representative. These men reach large numbers of health professionals. Thus they could be—and at times actually are—disseminators of useful information. They could consistently serve a real educational function in their ability to discuss their products.

At present they do distribute printed material, brochures and pamphlets—some of it scientifically sound and therefore truly useful—as well as some excellent films produced by the pharmaceutical industry. When they function in this

s He a Source of Information?

Yes, with certain reservations. 'he average sales representative ıas a great fund of information ıbout the drug products he is re-ponsible for. He is usually able to ınswer most questions fully and ntelligently. He can also supply eprints of articles that contain a ;reat deal of information. Here, oo, I exercise some caution. I usu-lly accept most of the statements nd opinions that I find in the ›apers and studies which come rom the larger teaching facilities. : goes without saying that a physi-ian should also rely on other ources for his information on ›harmacology.

'raining of Sales Representatives

Ideally, a candidate for the ›osition as a sales representative f a pharmaceutical company hould be a graduate pharmacist vho has a questioning mind. I don't nink this is possible in every case, nd so it becomes the responsibility of the pharmaceutical company to train these individuals comprehensively. It is of very great importance that the detail man's knowledge of the product he represents be constantly reviewed as well as updated. This phase of the sales representative's education should be a major responsibility of the medical department of the pharmaceutical company.

I am certain that most of these companies take special care to give their detail men a great deal of information about the products they produce—information about indications, contraindications, side effects and precautions. Yet, although most of the detail men are well informed, some, unfortunately, are not. It might be helpful if sales representatives were reassessed every few years to determine whether or not they are able to fulfill their important function. Incidentally, I feel the same way about periodic assessments of everyone in the health care field, whether they be general practitioners, surgeons or salesmen.

Value of Sampling

I personally am in favor of limited sampling. I do not use sampling in order to perform clinical testing of a drug. I feel that drug testing should rightly be left to the pharmacology researcher and to the large teaching institutions where such testing can be done in a controlled environment.

I do not use samples as a "starter dose" for my patients. I do, however, find samples of drugs to be of value in that they permit me to see what the particular medication looks like. I get to see the various forms of the particular medication at first hand, and if it is in a liquid form I take the time to taste it. In that way I am able to give my patients more complete information about the particular medications that I prescribe for them.

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apacity they are indeed useful; ›articularly in the fact that they lisseminate broadly based educa-ional material and serve not just s "pushers" of their drugs.

he Other Side of the Coin

Obviously, the pharmaceuti-al companies are not producing all ıis material as a labor of love—ıey are in the business of selling roducts for profit. In this regard ıe ambitious and improperly moti-ated sales representative can xert a negative influence on the racticing physician, both by pre-enting a one-sided picture of his roduct, and by encouraging the ractitioner to depend too heavily n drugs for his total therapy. In hese ways, the salesman has often listorted objective reality and ındermined his potential role as an ducator.

'he Industry Responsibility

Since the detail man must be ın information resource as well as ı representative of his particular ›harmaceutical company, he hould be carefully selected and thoroughly trained. That training, perforce, must be an ongoing one. There must be a continuing battle within and with the pharmaceutical industry for high quality not only in the selection and training of its sales representatives, but also in the development of all of its promotional and educational material.

The industry must be ready to accept constructive as well as corrective criticism from experts in the field and consumer spokesmen, and be willing to accept independent peer review. The better educated and prepared the salesman is, the more medically accurate his materials, the better off the pharmaceutical industry, health professionals and the public—*i.e.*, the patients—will be.

Physician Responsibility

The practicing physician is in constant need of up-dated information on therapeutics, including drugs. He should and does make use of drug information and answers to specific questions supplied by the pharmaceutical representative. However, that information must not be his main source of continuing education. The practitioner must keep up with what is current by making use of scientific journals, refresher courses, and information received at scientific meetings.

The practicing physician not only has the right, but has the responsibility to demand that the pharmaceutical company and its representatives supply a high level of valid and useful information. I feel certain that if such a high level is demanded by the physician as well as the public, this demand will be met by an alert and concerned pharmaceutical industry.

From my experience, my impression is that sectors of the pharmaceutical industry are indeed ethical. I challenge the industry as a whole to live up to that word in its finest sense.

Pharmaceutical Manufacturers Association
1155 Fifteenth Street, N.W.
Washington, D.C. 20005

P·M·A

CONTINUING MEDICAL EDUCATION

California, Hawaii • Oregon • Washington, Montana, Alaska, Idaho

CALIFORNIA and HAWAII

COMMITTEE ON CONTINUING MEDICAL EDUCATION

THIS BULLETIN of information regarding continuing education programs and meetings of various medical organizations in **California and Hawaii** is supplied by the Committee on Continuing Medical Education of the California Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Committee on Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103; or phone (415) 777-2000. Note: Please see **California Medicine**, Vol. 117, No. 4, October, 1972 issue for a list of organizations approved for Category I Credit toward the CMA Certificate in Continuing Medical Education.

ALCOHOL AND DRUG ABUSE

February 13—**Alcohol and Drugs.** USC. Thursday.

CANCER

January 22—**Carcinoma of the Oral Cavity—Second Annual Central Valley Medical Conference.** American Cancer Society at Holiday Inn, Modesto. Wednesday. Contact Dr. Fredrick Mantz, P.O. Box 285, Modesto 95353. (209) 522-5238.

January 29—**Advances in Cancer Diagnosis.** American Cancer Society, Long Beach-Harbor-Southeast Unit, at Center for Health Education, Memorial Hospital Medical Center, Long Beach. Wednesday. 7 hrs. $35; $15, residents. Contact: Philip King, Ed. Dir., ACS, 936 Pine Ave., Long Beach 90813. (213) 437-0791.

January 29—**Intensive Chemotherapy of Malignant Neoplasia.** Hospital of the Good Samaritan and American Cancer Society at Hosp. of Good Samaritan, Los Angeles. Wednesday. 6½ hrs. $40. Contact: Janie Sternal, Coord., Cont. Med. Ed., Hosp. of the Good Samaritan, 1212 Shatto St., L.A. 90017. (213) 482-8111.

February 27-March 2—**Seminar on Modern Concepts in Oncology—3rd Annual.** UCLA. Thursday-Sunday.

February 28—**Cancer of the Head and Neck.** American Cancer Society, Kern County Unit, at Bakersfield Inn, Bakersfield. Friday. 7 hrs. $25. Contact: Donald C-S Tan, MD and/or Phillip Mahans, DDS, Co-Chairmen, 238 18th St., Bakersfield 93301. (805) 325-5117.

March 20-21—**Clinical Cancer Conference—10th Annual.** UCSF at St. Francis Hotel, San Francisco. Thursday-Friday.

MEDICINE

January 16-18—**The Respective Roles of Medicine and Surgical Treatment in Cardiac Disease in the Adult.** American College of Physicians, UCLA, Cedar-Sinai Medical Center at Century Plaza Hotel, Los Angeles. Thursday-Saturday. $100 for ACP members; $150, non-members. Contact: Registrar, Postgraduate Courses, 4200 Pine St., Philadelphia, Pa. 19104. (215) 222-8120.

January 17-18—**Colonoscopy.** American and Southern Calif. Societies for Gastrointestinal Endoscopy at Beverly Hilton Hotel, Bevery Hills. Friday-Saturday. 9 hrs. $65 for members; $90, non-members. Contact: Melvin Schapiro, MD, 5400 Balboa Blvd., No. 202, Encino 91316. (213) 981-1300.

January 24-25—**Medical Application of Behavior Modification.** See Psychiatry, January 24-25.

January 26-February 1—**Skiers' Symposium: Pre-, Intra- and Post-Operative Management of the Surgical Patient.** See Of Interest To All, January 26-February 1.

January 29—**Pediatric Dermatology.** See Pediatrics, January 29.

January 29-31—**Pediatric Dermatology.** See Pediatrics, January 29-31.

February 5—**Cardiac Diagnostic Techniques.** Charles R. Drew Postgraduate Medical School at Martin Luther King, Jr., General Hospital, Los Angeles. Wednesday. Contact: Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 E. 120th St., Los Angeles 90059. (213) 564-5911, ext. 391.

February 7—**Stomatology.** STAN. Friday.

February 10-14—**Infectious Disease.** STAN and American College of Physicians at Squaw Valley. Monday-Friday.

February 12-14—**Diabetes and Related Endocrine Diseases.** UCSF. Wednesday-Friday.

February 15—**Abnormal Lab Data: Hypertension.** See Radiology and Pathology, February 15.

KEY TO ABBREVIATIONS AND SYMBOLS

Medical Centers and CMA Contacts for Information

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103. (415) 777-2000.

LLU: Loma Linda University
Contact: John E. Peterson, MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311.

PMC: Pacific Medical Center
Contact: Allen J. Enelow, MD, Chairman, Education Committee, Pacific Medical Center, P.O. Box 7999, San Francisco 94120. (415) 563-4321.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Neil C. Andrews, MD, Chairman, Department of Postgraduate Medicine, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, California College of Medicine, Irvine
Contact: Robert Combs, MD, Associate Dean, Continuing Medical Education, University of California, Irvine—California College of Medicine, Irvine 92664. (714) 833-5991.

UCLA: University of California, Los Angeles
Contact: Donald Brayton, MD, Director Continuing Education in Medicine and the Health Sciences. P.O. Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: Richard A. Lockwood, MD, Associate Dean for Health Manpower, 1310 Basic Sciences Building, University of California, San Diego, School of Medicine, La Jolla 92037. (714) 453-2000, ext. 1251.

UCSF: University of California, San Francisco
Contact: Malcolm S. M. Watts, MD, Associate Dean and Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-2342.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 226-2047.

February 15-19—**American Academy of Allergy.** Town and Country Hotel, San Diego. Saturday-Wednesday. Contact: Janice Manke, AAA, 225 E. Michigan St., Milwaukee, Wis. 53202. (415) 272-6071.

February 19—**Cardiopulmonary Resuscitation.** Charles R. Drew Postgraduate Medical School at Martin Luther King, Jr., General Hospital, Los Angeles. Wednesday. Contact: Office of Continuing Education, Drew Postgraduate Medical School, 1621 E. 120th St., Los Angeles 90059. (213) 564-5911, ext. 391.

February 21-22—**American College of Physicians, Southern California Regional Meeting.** Convention Center, Los Angeles. Friday-Saturday. Contact: Walter P. Martin, MD, 21510 S. Main St., Carson 90745.

February 26-28—**Acute Respiratory Care.** California Thoracic Society at Beverly Hilton Hotel, Beverly Hills. Wednesday-Friday. 21 hrs. $135 for CTS members; $160, others. Contact: Mrs. Laurie Harkess, Prog. Asst., CTS, 224 Pendleton Way, Oakland 94621. (415) 636-1756.

February 27-28—**Endocrinology.** USC at Good Samaritan Hospital, Los Angeles. Thursday-Friday.

February 27-28—**Dermatology for Internists and GPs.** UCSF. Thursday-Friday.

March 1—**Echocardiography Workshop.** PMC. Saturday. $65.

March 4—**Cutaneous Medicine.** USC. Tuesday.

March 6-8—**Cardiovascular Disease—1975: Practical Diagnosis and Management.** American College of Cardiology at Sheraton Harbor Island Hotel, San Diego. Thursday-Saturday. Contact: Mary Anne McInerny, Dir., Dept. of Cont. Ed. Programs, 9650 Rockville Pike, Bethesda, Md. 20014. (301) 530-1600.

March 7—**Diabetes.** USD at Sacramento Inn, Sacramento. Friday.

March 10-14—**Electrophysiology.** USC at Canyon Club, Palm Springs. Monday-Friday.

March 13-14—**Core Curriculum: Cardiovascular Physiology: Clinical Utilization of Invasive and Non-Invasive Measurements.** American College of Cardiology and UCLA at Cedars of Lebanon Hospital, Los Angeles. Thursday-Friday. Contact: Mary Anne McInerny, Dir., Dept. of Cont. Ed. Programs, ACC, 9650 Rockville Pike, Bethesda, Md. 20014. (301) 530-1600.

March 13-15—**Cardiology '75.** American Heart Association, Golden Empire Chapter, at Sahara Tahoe Hotel, South Lake Tahoe. Thursday-Saturday. Contact: Nemat O. Borhani, MD, P.O. Box 16011, Sacramento 95816.

March 20-21—**Arthritis and Clinical Immunology.** USC. Thursday-Friday.

March 27-29—**Recent Advances in Coronary Heart Disease.** UCI and Pasadena Cardiovascular Research Foundation at Balboa Bay Club, Newport Beach. Thursday-Saturday.

March 31-April 11—**Intensive Review of Internal Medicine.** USC. Two weeks.

MENTAL RETARDATION

March 9-21—**Mental Retardation.** UCLA. 13 days.

OBSTETRICS AND GYNECOLOGY

January 17-18—**Colposcopy.** Charles R. Drew Postgraduate Medical School at Airport Hyatt House (17) and Martin Luther King, Jr., General Hospital (18), Los Angeles. Friday-Saturday. Contact: Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 E. 120th St., Los Angeles 90059. (213) 564-5911, ext. 391.

January 27-28—**Neonatal Respiratory Symposium.** USC at Marriott Hotel, Los Angeles. Monday-Tuesday. Will reconvene in Aspen, Colo., January 29-31. Contact: John S. McDonald, MD, Dir., Perinatal Anesthesia, P.O. Box 54508, Los Angeles 90054.

January 27-30—**Perinatal Medicine.** USC at Kona Surf Hotel, Kona, Hawaii. Monday-Thursday. $180.

February 8-9—**Obstetrical and Gynecological Forum.** Los Angeles Obstetrical & Gynecological Society at Beverly Hilton Hotel, Los Angeles. Saturday-Sunday. $40 for physicians; $15, residents. Contact: Miss Dee Davis, Exec. Sec., 5410 Wilshire Blvd., Los Angeles 90036. (213) 931-1621.

February 10-12—**The Heart, Lungs and Circulation in the Fetus and Newborn.** UCSF at Union Square Hyatt Hotel, San Francisco. Monday-Wednesday.

March 7-8—**Current Topics in Contraception: The Pill vs. IUD.** PMC. Friday-Saturday.

March 25-28—**High Risk Pregnancy.** USC at Canyon Hotel, Palm Springs. Tuesday-Friday.

March 28-29—**Review of Gynecological Surgery.** PMC. Friday-Saturday.

PEDIATRICS

January 24-26—**Pediatric Anesthesiology.** See Surgery and Anesthesiology, January 24-26.

January 29—**Pediatric Dermatology.** USC at Womens Hospital, Los Angeles. Wednesday.

January 29-31—**Pediatric Dermatology.** STAN and American Academy of Pediatrics at Holiday Inn, Palo Alto. Wednesday-Friday.

January 30—**The Battered Child.** USC at Casa Royal, Bakersfield. Thursday.

January 30—**Parmelee Memorial Lecture—14th Annual.** Los Angeles Pediatric Society; American Academy of Pediatrics, California Chapter 2, at Los Angeles County Medical Association, Los Angeles. Thursday. Contact: L.A. Pediatric Society, P.O. Box 2022, Inglewood 90305. (213) 757-1198.

February 10-12—**The Heart, Lungs and Circulation in the Fetus and Newborn.** See Ob-Gyn, February 10-12.

March 7-9—**Clinical Pediatrics—5th Annual Southern California Pediatric Postgraduate Course.** Am. Academy of Ped., Chapter II, Dist. 9; Childrens Hosp. of L.A.; L.A. Ped. Soc.; Southwest Ped. Soc.; Childrens Hosp. of Orange Co. at Riviera Hotel, Palm Springs. Friday-Sunday. $75. Contact: Robert M. Romans, MD, c/o Lili Crellin, Resident's Office, Childrens Hospital, 4650 Sunset Blvd., L.A. 90027.

March 8-9—**Health of the School Child.** UCSF. Saturday-Sunday.

PSYCHIATRY

January 15-April 2—**Advanced Psychotherapeutic Techniques—A Practical Approach to Therapy.** UCLA. Wednesday evenings; 12 sessions.

January 24-25—**Medical Application of Behavior Modification.** PMC. Friday-Saturday.

January 25-26—**Autism: Diagnosis, Current Research and Management.** UCLA. Saturday-Sunday.

February 2-7—**Midwinter Program for Psychiatrists.** UCD at Squaw Valley Lodge, Squaw Valley. Sunday-Friday.

February 28-March 1—**Community Mental Health.** USC at Continental Hyatt House, Hollywood. Friday-Saturday. 10 hrs. $60. Contact: Donald H. Naftulin, MD, Dir., Cont. Ed. in Psych., USC. (213) 226-2114.

RADIOLOGY AND PATHOLOGY

January 26-28—**Genitourinary Pathology.** UCI at Memorial Hospital Medical Center, Long Beach. Sunday-Tuesday.

January 31-February 2—**Los Angeles Midwinter Radiological Conference—27th Annual.** Los Angeles Radiological Society at Century Plaza Hotel, Los Angeles. Friday-Sunday. Contact: James F. Mack, MD, St. Mary's Hospital, 509 E. 10th St., Long Beach 90813.

February 5—**Cardiac Diagnostic Techniques.** See Medicine, February 5.

February 5-7—**1975 San Diego Biomedical Symposium.** UCSD at Hilton Inn, Mission Bay, San Diego. Wednesday-Friday. Contact: Dr. Lowell Rosen, Prog. Chr., Dept. of Radiology, UCSD, Box 109, La Jolla 92037. (714) 453-2000, ext. 2268.

February 15—**Abnormal Lab Data: Hypertension.** PMC. Saturday.

February 15-16—**Diagnostic Nuclear Imaging: A Review and What's New.** UCSF at Fairmont Hotel, San Francisco. Saturday-Sunday.

February 17-21—**Diagnostic Radiology.** UCSF at Fairmont Hotel, San Francisco. Monday-Friday.

February 22-23—**A Practical Course in Ultra Sound.** UCSF at Fairmont Hotel, San Francisco. Saturday-Sunday.

March 25-28—**Radiology.** USC at Canyon Hotel, Palm Springs. Tuesday-Friday.

SURGERY AND ANESTHESIOLOGY

January 16-18—**The Respective Roles of Medical and Surgical Treatment in Cardiac Disease in the Adult.** See Medicine, January 16-18.

January 17-18—**Colonoscopy.** See Medicine, January 17-18.

January 19—**Orthopaedic Surgery and Surgical Anatomy of the Wrist and Hand.** International College of Surgeons, U.S. Section, at Los Angeles Orthopaedic Hospital, Los Angeles. Sunday. 8 hrs. $50. Contact: Irving Rehman, PhD, Chr., Postgraduate & Ongoing Education Committee, 5153 Tampa Ave., Tarzana 91356. (213) 344-3305.

January 20-23—**Midwinter Clinical Convention for Ophthalmology and Otolaryngology.** The Research Study Club of Los Angeles, Inc., at Hilton Hotel, Los Angeles. Monday-Thursday. 28 hrs. Contact: Russell M. Decker, MD, P.O. Box 49412, Los Angeles 90049.

January 24-26—**Pediatric Anesthesiology—13th Clinical Conference.** Children's Hospital of Los Angeles at Marriott Hotel, Los Angeles. Friday-Sunday. 15 hrs. $100. Contact: Wayne Herbert, MD, Division of Anesthesiology, Children's Hospital, P.O. Box 54700, L.A. 90054.

January 26-28—**Refresher Course in Urology.** UCI at Center for Health Education, Long Beach. Sunday-Tuesday. Contact: Chuck Paul, UCI, Dept. UNEX, Irvine 92664. (714) 833-5193.

January 26-February 1—**Skiers' Symposium: Pre-, Intra- and Post-Operative Management of the Surgical Patient.** See Of Interest To All, January 26-February 1.

January 29-31—**Advances in Neurology.** UCSF. Wednesday-Friday.

January 31—**Difficult Problems about the Shoulder, Arm and Elbow.** American Academy of Orthopaedic Surgeons at Biltmore Hotel, Santa Barbara. Friday. Contact: Dean A. Smith, MD, Santa Barbara Medical Foundation Clinic, P.O. Box 1200, Santa Barbara 93102.

February 1—**Symposium on Acutely Injured Patient.** International College of Surgeons, So. Calif. Division, at Hollywood Presbyterian Medical Center. Saturday. Contact: M. Hadi Salem, MD, 136 N. Brighton, Burbank 91506. (213) 846-0669.

February 2-5—**Theodor Billroth Course in Surgical Anatomy—16th Annual.** LLU. Sunday-Wednesday.

February 13-14—**Phaco-Fragmentation.** UCSF. Thursday-Friday.

February 15—**Sports Injuries to the Knee.** Charles R. Drew Postgraduate Medical School at Martin Luther King, Jr., General Hospital, Los Angeles. Saturday. Contact: Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 E. 120th St., Los Angeles 90059. (213) 564-5911, ext. 391.

February 15—**Surgical Anatomy and Surgery of the Neck.** International College of Surgeons, U.S. Section, at L.A. Orthopaedic Hospital, Los Angeles. Saturday. 8 hrs. $50. Contact: Irving Rehman, PhD, Chr., Postgraduate & Ongoing Education Committee, 5153 Tampa Ave., Tarzana 91356. (213) 344-3305.

February 15-21—**Pan-Pacific Surgical Association—13th Congress.** Hilton Hawaiian Village Hotel, Honolulu. Saturday-Friday. 22½ hrs. Contact: Robert A. Rose, MD, Sec. Gen., Pan-Pacific Surgical Assn., 236 Alexander Young Building, Honolulu 96817. (808) 536-4911.

February 19—**Cardiopulmonary Resuscitation.** See Medicine, February 19.

February 19-21—**Critical Care Medicine and Circulatory Shock.** See Of Interest to All, February 19-21.

February 23-March 7—**Temporal Bone Surgical Dissection Course.** Ear Research Institute, Los Angeles. Two weeks. $1,200; $900 for residents. Contact: Jack L. Pulec, MD, Ear Research Institute, 2130 W. 3rd St., Los Angeles 90057.

February 26-28—**Acute Respiratory Care.** See Medicine, February 26-28.

February 27-March 1—**American Society for Surgery of the Hand—Annual Meeting.** Fairmont Hotel, San Francisco. Thursday-Saturday. $50. Contact: John A. Boswick, Jr., MD, 4200 E. 9th Ave., #2414, Denver 80220. (303) 394-8549.

February 28-March 2—**Harry Benjamin 4th International Conference on Gender Identity.** STAN. Friday-Sunday.

March 1—**American Orthopaedic Foot Society—Annual Scientific Meeting.** Civic Auditorium, San Francisco. Saturday. Contact: Henry R. Cowell, MD, Box 269, Wilmington, Dela. 19805. (302) 571-1000.

March 1-6—**American Academy of Orthopaedic Surgeons.** Brooks Hall, Civic Auditorium, San Francisco. Friday-Wednesday. Contact: Charles V. Heck, MD, Exec. Dir., AAOS, 430 N. Michigan Ave., Chicago, Ill. 60611. (312) 822-0970.

March 11-15—**Symposium on Vascular Surgery—3rd Annual.** UCLA at Canyon Hotel, Palm Springs. Tuesday-Saturday.

March 12-15—**Neurosurgical Society of America.** Rancho Bernardo, San Diego. Wednesday-Saturday. Contact: Shelley N. Chou, MD, U. of Minn. Medical School, Minneapolis, Minn. 55455.

March 13-14—**Phaco-Fragmentation.** UCSF. Thursday-Friday.

March 15—**Surgical Anatomy and Surgery of the Abdomen.** International College of Surgeons, U.S. Section, at L.A. Orthopaedic Hospital, Los Angeles. Saturday. 8 hrs. $50. Contact: Irving Rehman, PhD, Chr., Postgraduate & Ongoing Education Committee, 5153 Tampa Ave., Tarzana 91356. (213) 344-3305.

March 15-16—**Los Angeles County Society of Anesthesiologists—20th Annual Postgraduate Assembly.** Hilton Hotel, Los Angeles. Saturday-Sunday. Contact: L.A. County Soc. of Anesthesiologists, 184 N. Canon Dr., Beverly Hills 90210.

March 15-19—**Controversial Areas in Surgery—12th Annual.** UCLA at Canyon Hotel, Palm Springs. Saturday-Wednesday.

March 16-28—**Temporal Bone Surgical Dissection Course.** Ear Research Institute, Los Angeles. Two weeks. $1,200; $900, residents. Contact: Jack L. Pulec, MD, 2130 W. 3rd St., L.A. 90057.

March 17-18—**G. Mosser Taylor Course in Orthopedic Surgical Anatomy—The Lower Extremity.** LLU. Monday-Tuesday.

March 19-23—**Management of Trauma.** UCLA at Canyon Hotel, Palm Springs. Wednesday-Sunday.

March 20-21—**Diseases of the Urinary Tract: Techniques and Principles of Urologic Surgery—3rd Annual Symposium.** STAN. Thursday-Friday.

March 21—**Cerebral Vascular Disease.** PMC. Friday.

OF INTEREST TO ALL PHYSICIANS

January 14-April 22—**Acupuncture for Management of Musculo-Skeletal Pain.** UCLA. Mondays, 7-10 p.m.

January 23-24—**Environmental Health and Safety in Health Care Facilties. UCSF.** Thursday-Friday.

January 26-February 1—**Skiers' Symposium: Pre-, Intra- and Post-Operative Management of the Surgical Patient.** Bernard Levinson, MD, Carmichael, Symposium Coordinator. Snowbird-Alta, Utah. Sunday-Saturday. Contact: Daman-Nelson Travel Agency, 115 Mission St., San Francisco. (415) 434-2018.

January 27-28—**Infection Control Workshop.** Marian Hospital; Infectious Disease Section, Calif. Dept. of Health; Santa Barbara Co. Health Dept.; Santa Barbara Lung Assn. at Marian Hospital, Santa Maria. Monday-Tuesday. Contact: Evelyn S. Zukerberg, RN, Asst. Admin., Marian Hosp., 1400 E. Church St., P.O. Box 1238, Santa Maria 93454. (805) 922-5811.

January 27-31—**Topics in Emergency Medicine.** UCSF. Monday-Friday.

January 29-February 1—**Physician and the Hospital.** USC at Ahwahnee Hotel, Yosemite. Wednesday-Saturday.

February 1—**Symposium on Acutely Injured Patient.** See Surgery, February 1.

February 3-8—**Family Practice Refresher Course—6th Annual.** UCI at Newporter Inn, Newport Beach. Monday-Saturday.

February 5-7—**Physicians in Family Practice—25th Annual Course.** Mt. Zion Hospital and Medical Center, San Francisco. Wednesday-Friday. Contact: Ms. Ann Raisbeck, Asst. to Dir. of Med. Education, Mt. Zion Hosp. & Med. Center, 1600 Divisadero St., San Francisco 94115. (415) 567-6600.

February 12—**Team Techniques in Management of Speech Problems in the Cleft Palate Patient.** Cleft Palate Team, Rancho Los Amigos Hosp.; USC; L.A. Co. National Foundation March of Dimes at Rancho Los Amigos Hospital, Downey. Wednesday. $15. Contact: Libby Wilson, MD, Rancho Los Amigos Hospital, 7601 E. Imperial Highway, Downey 90242.

February 16-19—**Society of Critical Care Medicine.** Anaheim. Sunday-Wednesday. Contact: David Allan, MD, Children's Memorial Hospital, 2300 Children's Plaza, Chicago, Ill. 60614.

February 19-21—**Critical Care Medicine and Circulatory Shock.** USC at Anaheim Convention Center, Anaheim. Wednesday-Friday.

February 21-22—**The Process and Treatment of Aging.** Vista Hill Foundation at Hilton Inn, San Diego. Friday-Saturday. $35; $20 for students and interns. Contact: Keith S. Ditman, MD, Vista Hill Foundation, 7798 Starling Dr., Suite 206, San Diego 92123. (714) 278-6761.

February 21-22—**Emergency Care.** UCD at Sahara Club, So. Lake Tahoe. Friday-Saturday.

February 21-26—**California Medical Association—104th Annual Session.** Los Angeles Convention Center. Friday-Wednesday.

February 27-28—**Dermatology for Internists and GPs.** See Medicine, February 27-28.

February 28-March 2—**Harry Benjamin 4th International Conference on Gender Identity.** See Surgery, February 28-March 2.

March 3-7—**Basic Science for Clinicians.** STAN. Monday-Friday.

March 9-13—**LLU Alumni Postgraduate Convention.** Sunday-Thursday. 23 hrs. $100. Contact: Gerald W. Miller, Gen. Chr., 1832 Michigan, Los Angeles. (213) 262-2173.

March 13-16—**Continuing Education in the Physician's Office.** USC at Mayer Auditorium, Palm Springs. Thursday-Sunday.

March 21-22—**West Coast Counties Postgraduate Institute.** CMA at Quail Lodge, Carmel. Friday-Saturday.

March 23-27—**American Association of Anatomists.** Hilton Hotel, Los Angeles. Sunday-Thursday. Contact: Dr. Melvin Hess, Dept. of Anatomy, La. State Univ. Med. Center, 1542 Tulane Ave., New Orleans, La. 70112.

PRECEPTORSHIPS AND TRAINEESHIPS

Training for Physicians in General Internal Medicine. LLU. Four weeks or more, by arrangement. Bedside and classroom training, practical aspects of clinical care and management. 160 hrs. Contact: LLU.

Training of Physicians in Modern Concepts of Pulmonary Care. LLU. Four weeks or more, by arrangement. Diagnostic and therapeutic methods in medical chest disease, physiological methodology of modern pulmonary care programs, use of new instrumentation in the field. 160 hrs. Contact: John E. Hodgkin, MD, LLU.

Training for Physicians in Nephrology. LLU. Four weeks or more, by arrangement. Hemodialysis, peritoneal displays, renal biopsy, and kidney transplantation. 160 hrs. Contact: Robert E. Soderblom, MD, LLU.

Mini Residencies in Orthopaedics. STAN. Postgraduate traineeships of 4-14 days, as you wish. No tuition but donations accepted. Contact: Orthopaedic Division, Dept. of Surgery, Stanford.

Preceptorships in Cardiology. PMC. By arrangement. $200 per mo.; $500 for 3 mos. Contact: Arthur Selzer, MD, PMC.

Preceptorships in Practical Office Dermatology. PMC. Wednesdays or Fridays, 9:00 a.m.-12:00 noon, for 10 weeks. Periods begin Oct., Jan., or April. $100. Contact: Harold M. Schneidman, MD, Dept. of Dermatology, PMC.

Preceptorships in Infectious Disease. PMC. Full time for four weeks. To be arranged. $250. Contact: Rodney J. Valentine, MD, Chief, Div. of Infectious Diseases, PMC.

Preceptorships in Basic Sciences, Biochemistry and Biophysics, Dermatology, International Health, Microbiology, Neurological Surgery, Obstetrics and Gynecology, Pediatrics, Pharmacology and Experimental Therapeutics, Physiology, Psychiatry, Urology. UCSF. By special arrangement.

Traineeships in Renal Dialysis. UCSF. By special arrangement.

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(Continued on Page 47)

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For more than thirty years PREMARIN (Conjugated Estrogen Tablets, U.S.P.) has been prepared with natural equine estrogens exclusively—without synthetic estrogen supplements. For more than thirty years it has provided the complete estrogen complex in the proportions found in its natural source. And for more than thirty years PREMARIN has enjoyed an unparalleled record of clinical efficacy and acceptance.

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BRIEF SUMMARY
(For full prescribing information, see package circular.)
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Indications: Based on a review of PREMARIN Tablets by the National Academy of Sciences-National Research Council and/or other information, FDA has classified the indications for use as follows:
Effective: As replacement therapy for naturally occurring or surgically induced estrogen deficiency states associated with: the climacteric, including the menopausal syndrome and postmenopause; senile vaginitis and kraurosis vulvae, with or without pruritus.
"Probably" effective: For estrogen deficiency-induced osteoporosis, and only when used in conjunction with other important therapeutic measures such as diet, calcium, physiotherapy, and good general health-promoting measures. Final classification of this indication requires further investigation.

Contraindications: Short acting estrogens are contraindicated in patients with (1) markedly impaired liver function; (2) known or suspected carcinoma of the breast, except those cases of progressing disease not amenable to surgery or irradiation occurring in women who are at least 5 years postmenopausal; (3) known or suspected estrogen-dependent neoplasia, such as carcinoma of the endometrium; (4) thromboembolic disorders, thrombophlebitis, cerebral embolism, or in patients with a past history of these conditions; (5) undiagnosed abnormal genital bleeding.
Warnings: Estrogen therapy should not be given to women with recurrent chronic mastitis or abnormal mammograms except, if in the opinion of the physician, it is warranted despite the possibility of aggravation of the mastitis or stimulation of undiagnosed estrogen-dependent neoplasia.

The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, retinal thrombosis, cerebral embolism and pulmonary embolism). If these occur or are suspected, estrogen therapy should be discontinued immediately.

Estrogens may be excreted in the mother's milk and an estrogenic effect upon the infant has been described. The long range effect on the nursing infant cannot be determined at this time.

Hypercalcemia may occur in as many as 15 percent of breast cancer patients with metastases, and this usually indicates progression of bone metastases. This occurrence depends neither on dose nor on immobilization. In the presence of progression of the cancer or hypercalcemia, estrogen administration should be stopped.

A statistically significant association has been reported between maternal ingestion of diethylstilbestrol during pregnancy and the occurrence of vaginal carcinoma in the offspring. This occurred with the use of diethylstilbestrol for the treatment of threatened abortion or high risk pregnancies. Whether or not such an association is applicable to all estrogens is not known at this time. In view of this finding, however, the use of any estrogen in pregnancy is not recommended.

Failure to control abnormal uterine bleeding or unexpected recurrence is an indication for curettage.
Precautions: As with all short acting estrogens, the following precautions should be observed:

A complete pretreatment physical examination should be performed with special reference to pelvic and breast examinations.

To avoid prolonged stimulation of the endometrium and breasts in climacteric or hypogonadal women, estrogens should be administered cyclically (3 week regimen with 1 week rest period—withdrawal bleeding may occur during rest period).

Because of individual variation in endogenous estrogen production, relative overdosage may occur which could cause undesirable effects such as abnormal or excessive uterine bleeding, mastodynia and edema.

Because of salt and water retention associated with estrogenic anabolic activity, estrogens should be used with caution in patients with epilepsy, migraine, asthma, cardiac, or renal disease.

If unexplained or excessive vaginal bleeding should occur, reexamination should be made for organic pathology.

Pre-existing uterine fibromyomata may increase in size while using estrogens; therefore, patients should be examined at regular intervals while receiving estrogenic therapy.

The pathologist should be advised of estrogen therapy when relevant specimens are submitted.

Because of their effects on epiphyseal closure, estrogens should be used judiciously in young patients in whom bone growth is incomplete.

Prolonged high dosages of estrogens will inhibit anterior pituitary functions. This should be borne in mind when treating patients in whom fertility is desired.

The age of the patient constitutes no absolute limiting factor, although treatment with estrogens may mask the onset of the climacteric.

Certain liver and endocrine function tests may be affected by exogenous estrogen administration. If test results are abnormal in a patient taking estrogen, they should be repeated after estrogen has been withdrawn for one cycle.
Adverse Reactions: The following adverse reactions have been reported associated with short acting estrogen administration:
nausea, vomiting, anorexia
gastrointestinal symptoms such as abdominal cramps and bloating
breakthrough bleeding, spotting, unusually heavy withdrawal bleeding (See DOSAGE AND ADMINISTRATION)
breast tenderness and enlargement
reactivation of endometriosis
possible diminution of lactation when given immediately postpartum
loss of libido and gynecomastia in males
edema
aggravation of migraine headaches
change in body weight (increase, decrease)
headache
allergic rash
hepatic cutaneous porphyria becoming manifest
Dosage and Administration: PREMARIN should be administered cyclically (3 weeks of daily estrogen and 1 week off) for all indications except selected cases of carcinoma and prevention of postpartum breast engorgement.

Menopausal Syndrome—1.25 mg. daily, cyclically. Adjust dosage upward or downward according to severity of symptoms and response of the patient. For maintenance, adjust dosage to lowest level that will provide effective control.

If the patient has not menstruated within the last two months or more, cyclic administration is started arbitrarily. If the patient is menstruating, cyclic administration is started on day 5 of bleeding. If breakthrough bleeding (bleeding or spotting during estrogen therapy) occurs, increase estrogen dosage as needed to stop bleeding. In the following cycle, employ the dosage level used to stop breakthrough bleeding in the previous cycle. In subsequent cycles, the estrogen dosage is gradually reduced to the lowest level which will maintain the patient symptom-free.

Postmenopause—as a protective measure against estrogen deficiency-induced degenerative changes (*e.g.* osteoporosis, atrophic vaginitis, kraurosis vulvae)—0.3 mg. to 1.25 mg. daily and cyclically. Adjust dosage to lowest effective level.

Osteoporosis (to retard progression)—usual dosage 1.25 mg. daily and cyclically.

Senile Vaginitis, Kraurosis Vulvae with or without Pruritus—0.3 mg. to 1.25 mg. or more daily, depending upon the tissue response of the individual patient. Administer cyclically.
How Supplied: PREMARIN (Conjugated Estrogens Tablets, U.S.P.)

No. 865—Each *purple* tablet contains 2.5 mg., in bottles of 100 and 1,000.

No. 866—Each *yellow* tablet contains 1.25 mg., in bottles of 100 and 1,000. Also in unit dose package of 100.

No. 867—Each *red* tablet contains 0.625 mg., in bottles of 100 and 1,000.

No. 868—Each *green* tablet contains 0.3 mg., in bottles of 100 and 1,000. 7352

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chlorzoxazone † 250 mg.; acetaminophen 300 mg.
*This drug has been evaluated as "probably" effective for this indication.
See brief summary of prescribing information on facing page for Indications, Contraindications, Warnings, Precautions and Adverse Reactions.
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PARAFON FORTE® tablets help relieve pain, restore mobility and stop pain-spasm feedback by providing:

a nonsalicylate analgesic equal to aspirin for relief of pain,[1,2] yet unlikely to cause the gastric irritation,[2,3] allergic reactions[2] or increased bleeding time[4] associated with aspirin therapy...

and a skeletal muscle relaxant shown in extensive clinical studies to afford relief of discomfort in acute musculoskeletal conditions*[5-7] but which is not an antihistamine or tranquilizer derivative and is unlikely to produce a tranquilizing or sedative effect.[5,7,8]

*Indications: Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:

"Probably" effective as an adjunct to rest and physical therapy for the relief of discomfort associated with acute, painful musculoskeletal conditions. The mode of action of this drug has not been clearly identified, but may be related to its sedative properties. Chlorzoxazone does not directly relax tense skeletal muscles in man.

Contraindications: Sensitivity to either component.
Warnings: *Usage in Pregnancy*—Use in women of childbearing potential only when potential benefits outweigh possible risks.
Precautions: Exercise caution in patients with known allergies or history of drug allergies. If a sensitivity reaction or any signs or symptoms suggestive of liver dysfunction are observed, the drug should be stopped.
Adverse Reactions: Occasionally, drowsiness, dizziness, lightheadedness, malaise, overstimulation or gastrointestinal disturbances may be noted; rarely, allergic-type skin rashes, petechiae, ecchymoses, angioneurotic edema or anaphylactic reactions. In rare instances, chlorzoxazone may possibly have been associated with gastrointestinal bleeding. While PARAFLEX® (chlorzoxazone) tablets and other chlorzoxazone-containing products have been suspected as being the cause of hepatic toxicity in approximately twenty-four patients, it was not possible to state that the dysfunction was or was not drug induced.
Usual Adult Dosage: Two tablets q.i.d.
Supplied: Scored, light green tablets, imprinted "McNEIL"—bottles of 100.

References: 1. Batterman, R.C., and Grossman, A.J.: Fed. Proc. *14*:316, 1955. 2. Goodman, L.S., and Gilman, A., ed.: The Pharmacological Basis of Therapeutics, ed 4. New York, The Macmillan Company, 1970. 3. Vickers, F.N.: Gastroint. Endosc. *14*:94, 1967. 4. Mielke, C.H., Jr., and Britten, A.F.H.: New Engl. J. Med. *282*:1270, 1970 (Corresp.). 5. Vernon, W.G.: Curr. Therap. Res. *14*:801, 1972. 6. Scheiner, J.J.: Curr. Therap. Res. *14*:168, 1972. 7. Walker, J.M.: Curr. Therap. Res. *15*:248, 1973. 8. Data on file, McNeil Laboratories, Inc.

† U.S. Patent No. 2,895,877

McNEIL McNeil Laboratories, Inc.
Fort Washington, Pa. 19034

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OREGON

COUNCIL ON MEDICAL EDUCATION

THIS BULLETIN of information regarding continuing education programs and meetings of various medical organizations in Oregon is supplied by the Council on Medical Education of the Oregon Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Council on Medical Education, Oregon Medical Association, 2164 S.W. Park Place, Portland, Oregon 97205; or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

University of Oregon Medical School, Family Practice Center, 3181 S.W. Sam Jackson Park Road, Portland 97201:

Every Thursday, 8:00 a.m. to 9:00 a.m.—**Family Practice Grand Rounds.** Contact: David D. Smith, MD, Department of Family Practice, University of Oregon Medical School.

CARDIOLOGY

June 5-7—**Progress in Coronary Artery Disease and Valvular Heart Disease,** Portland. Contact: S. H. Rahimtoola, University of Oregon Medical School, 3181 S.W. Sam Jackson Park Road, Portland, 97201.

FAMILY PRACTICE

January 24—**Lederle Symposium,** Portland, Portland Sheraton Hotel. Contact: Ms. Skippie Patterson, Oregon Academy of Family Physicians, 2153 SW Main, Portland 97205, (503) 224-6966. Acceptable for 6 hours Category I credit.

February 9—**Practical Genetics for the Family Physician,** 9:00 a.m. to 5:00 p.m., Hilton Hotel, Portland. Contact: Neil Buist, MD, 429 S.W. Fourth Ave., Portland, 97204.

February 10-14—**General Family Practice Review,** Hilton Hotel, Portland. Contact: William Fisher, MD, University of Oregon Medical School, Department of Family Practice, 3181 S.W. Sam Jackson Park Road, Portland, 97201.

Every Thursday, 8:00 a.m. to 9:00 a.m.—**Family Practice Grand Rounds,** Family Practice Center, University of Oregon Medical School, Portland. Contact: David D. Smith, MD, Department of Family Practice, University of Oregon Medical School, 3181 S.W. Sam Jackson Park Road, Portland 97201.

OF INTEREST TO ALL PHYSICIANS

February 13-15—**13th Annual Chest Disease Conference,** Gleneden Beach, Salishan Lodge. Sponsored by Oregon Thoracic Society.

May 30-31—**Hypertension: The Challenge to the Clinician,** Portland, Jantzen Beach Thunderbird. Sponsored by the University of Oregon Medical School. Contact: M. Roberts Grover, Jr., MD, Associate Dean, University of Oregon Medical School, 3181 SW Sam Jackson Park Road, Portland 97201, (503) 225-8228. Acceptable for 10 hours Category I credit.

WASHINGTON, MONTANA, ALASKA and IDAHO

In order to have future activities listed here or to receive information on these and other activities, please write Ms. Joan M. Kelday, Information Specialist, Continuing Medical Education, WAMI Program, University of Washington School of Medicine, E-301, Health Sciences Building, SC-45, Seattle, Washington 98195. Phone: (206) 543-6995.

January 22-24—**Advances in Neurology.** Wednesday-Friday. Virginia Mason Medical Center Auditorium, Seattle. 18 hrs. $100, ACP members; $150, non-members; $50, ACP Associates. Contact: M. H. Jackson, Registrar, Postgraduate Courses, American College of Physicians, 4200 Pine St., Philadelphia, Pa., 19104.

January 24-25—**Tax, Estate and Financial Planning for Physicians.** Friday-Saturday. Seattle. $75. Contact: Richard L. Reimer, Asst. Dir. CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

January 26-February 1—**Advances in Perinatology.** Sunday-Saturday. Sun Valley, Idaho. 37½ hrs. $100 for physicians, $30 for nurses and other health professionals. Contact: Richard L. Reimer, Asst. Dir. CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

February 7-8—**A Modern Approach to Allergy.** Friday-Saturday. Virginia Mason Medical Center Auditorium, Seattle. 9 hrs. $50. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) MA 3-3700, Ext. 470.

February 19-20 — **Trauma-Burns-Shock: Emergency Medical Care—Univ. of Washington School of Medicine's Western Circuit Course.** Longview, Wash., Feb. 19; Olympia, Wash., Feb. 20. 4 hrs. $25. Contact: Richard L. Reimer, Asst. Dir. CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

February 20-21—**Thirteenth Annual Symposium on Respiratory Disease.** Thursday-Friday. Olympic Hotel, Seattle. Hours and fee not set. Contact: Richard L. Reimer, Asst. Dir. CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

February 28-March 1—**The Intensive Care Patient.** Friday-Saturday. Virginia Mason Medical Center Auditorium, Seattle. 9 hrs. $50. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) MA 3-3700, Ext. 470.

March 4-5—**Trauma-Burns-Shock: Emergency Medical Care—Univ. of Washington School of Medicine's Western Circuit Course.** Bremerton, Wash., Mar. 4; Bellingham, Wash., Mar. 5. 4 hrs. $25. Contact: Richard L. Reimer, Asst. Dir. CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

March 14-15—**Current Concepts in Cardiology.** Friday-Saturday. Virginia Mason Medical Center Auditorium, Seattle. 9 hrs. $50. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) MA 3-3700, Ext. 470.

March 17-21—**Emergency Medicine Institute.** Monday-Friday. Univ. of Wash. Health Sciences Center, Seattle. 40 hrs. $250. Contact: Richard L. Reimer, Asst. Dir. CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

March 20-21—**Basic Sciences for Clinicians.** Thursday-Friday. Univ. of Wash. Health Sciences Center, Seattle. Hours and fee not set. Contact: Richard L. Reimer, Asst. Dir. CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

March 31-April 4—**Advances in Family Practice.** Monday-Friday. Univ. of Wash. Health Sciences Center, Seattle. 40 hrs. $100. Contact: Richard L. Reimer, Asst. Dir. CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

April 4-5—**Acid Base and Blood Gas Management in the Surgical Patient.** Friday-Saturday. Virginia Mason Medical Center Auditorium, Seattle. 9 hrs. $50. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) MA 3-3700, Ext. 470.

April 10-11—**Developmental Disabilities: Early Identification and Intervention Can Make a Difference.** Thursday-Friday. Univ. of Wash. Health Sciences Center, Seattle. Hours and fee not set. Contact: Richard L. Reimer, Asst. Dir. CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

April 24-25—**Conference on Respiratory Care.** Thursday-Friday. Univ. of Wash. Health Sciences Center, Seattle. Hours not set. $75. Contact: Richard L. Reimer, Asst. Dir. CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

April 28-May 2—**Emergency Medicine Institute.** Monday-Friday. Univ. of Wash. Health Sciences Center, Seattle. 40 hrs. $250. Contact: Richard L. Reimer, Asst. Dir. CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

April 29-30—**Exercise Testing Workshop.** Tuesday-Wednesday. Univ. of Wash. Health Sciences Center, Seattle. Hours and fee not set. Contact: Richard L. Reimer, Asst. Dir. CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

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USDA's Four Food Groups categorizes foods according to their nutrients. Such a system makes it easier for your patients to follow a balanced diet.

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Potent Bronchodilation
ephedrine and theophylline relax bronchial musculature to open airways and keep them open.

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glyceryl guaiacolate helps liquefy tenacious secretions and enables productive cough to clear airways and keep them clear.

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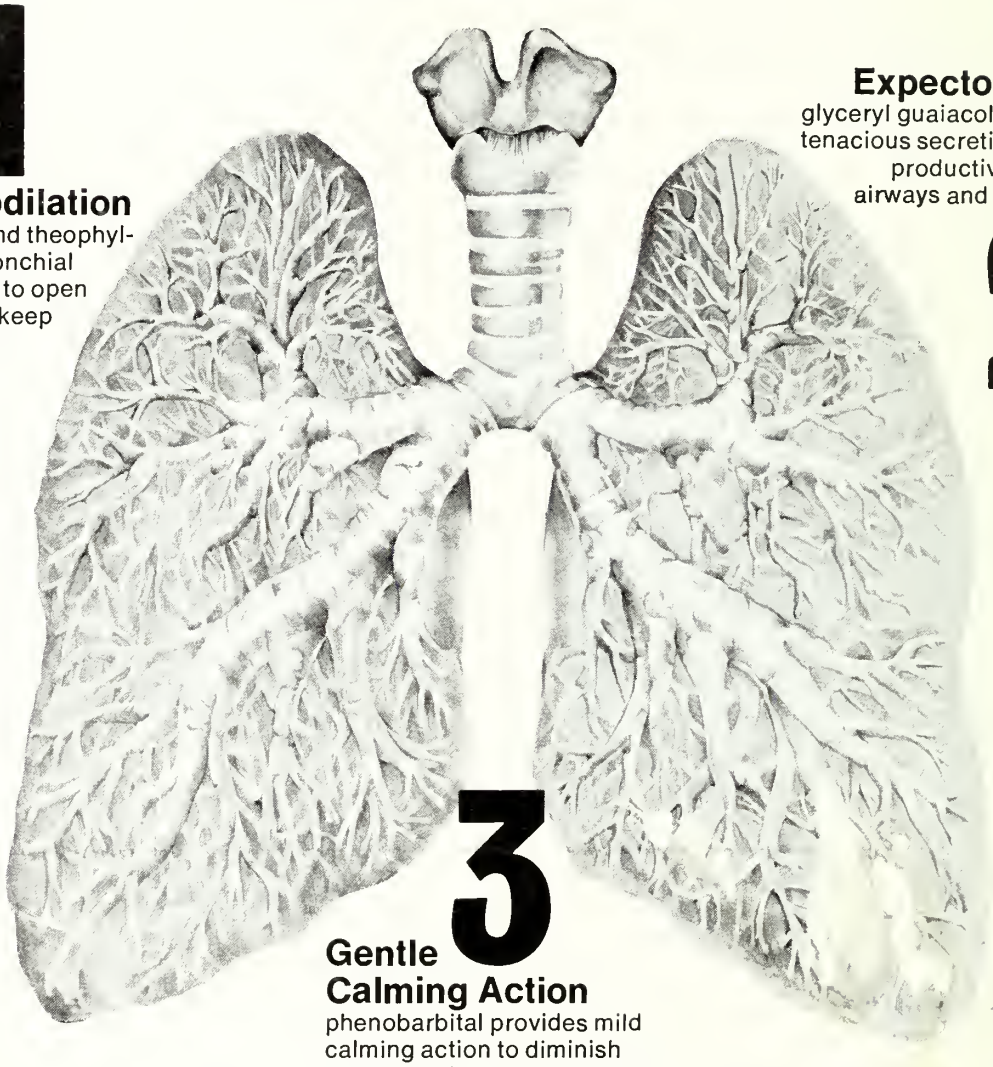

3

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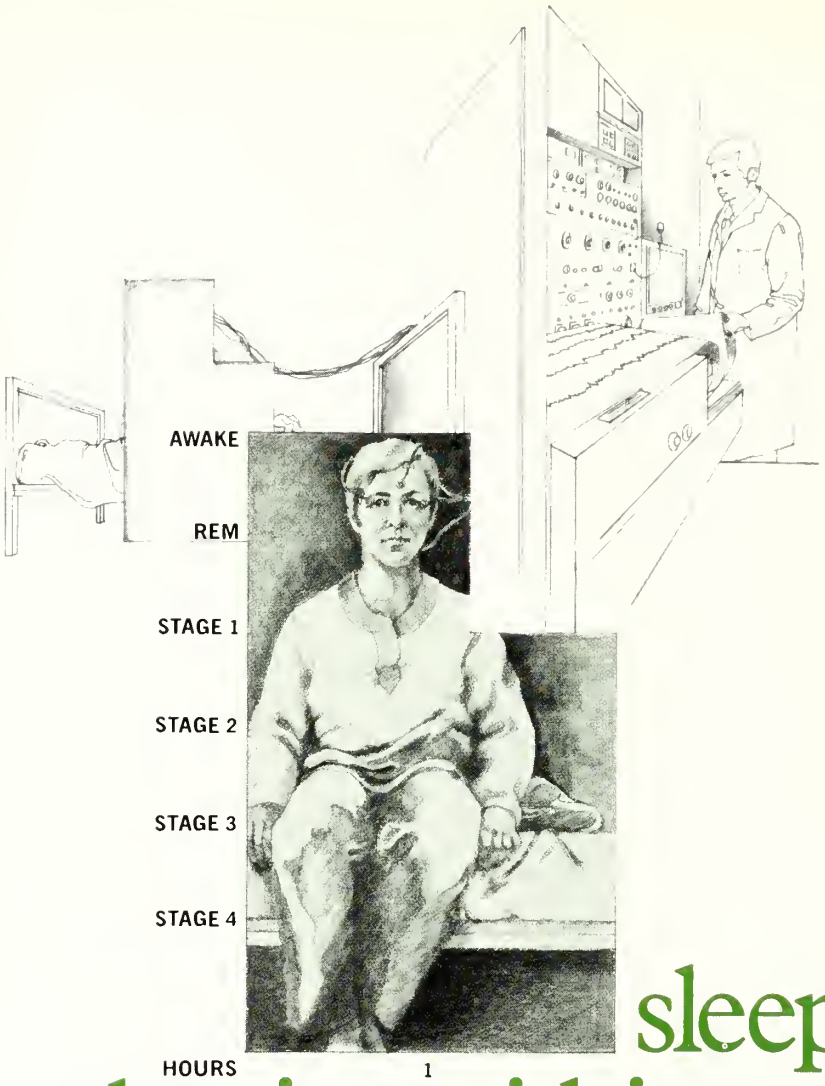

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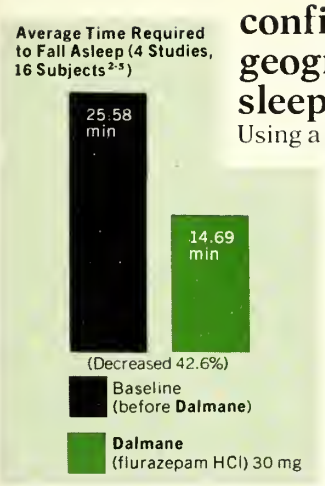
proved by a 22-night clinical study of insomnia patients in the sleep research laboratory and at home[1]

Three insomnia patients selected for difficulty falling asleep were administered Dalmane (flurazepam HCl) 30 mg for 14 consecutive nights. Placebo was given for four nights prior to and four nights after Dalmane. Physiologic tracings on Dalmane nights 1-3 showed sleep induction time averaged 13.90 minutes; on Dalmane nights 12-14, 18.80 minutes. Combined average for the 6 monitored drug nights was 16.35 minutes.[1]



confirmed by clinical studies in four geographically separated sleep research laboratories[2-5]

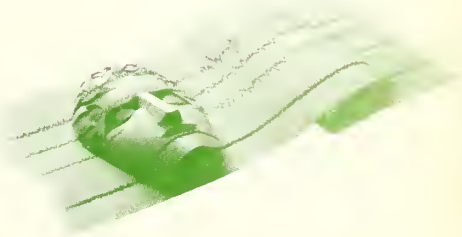
Using a 14-night protocol involving eight insomniac and eight normal subjects, four studies confirmed the sleep-inducing effectiveness of Dalmane (flurazepam HCl) and the reproducibility of this response. On average, one 30-mg capsule induced sleep within 17 minutes. In all these studies, Dalmane induced sleep rapidly, reduced nighttime awakenings, and provided 7 to 8 hours of sleep without repeating dosage.[2-5]

Dalmane (flurazepam HCl) induces and maintains sleep, with relative safety

Dalmane is generally well tolerated; morning "hang-over" has been relatively infrequent. While dizziness, drowsiness, lightheadedness and the like have been noted most often, particularly in the elderly and debilitated, physicians should be aware of the possibility of more serious reactions, as noted below.

Before prescribing Dalmane (flurazepam HCl), please consult Complete Product Information, a summary of which follows:

Indications: Effective in all types of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings and/or early morning awakening; in patients with recurring insomnia or poor sleeping habits; and in acute or chronic medical situations requiring restful sleep. Since insomnia is often transient and intermittent, prolonged administration is generally not necessary or recommended.
Contraindications: Known hypersensitivity to flurazepam HCl.
Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. Caution against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Use in women who are or may become pregnant only when potential benefits have been weighed against possible hazards. Not recommended for use in persons under 15 years of age. Though physical and psychological dependence have not been reported on recommended doses, use caution in administering to addiction-prone individuals or those who might increase dosage.
Precautions: In elderly and debilitated, initial dosage should be limited to 15 mg to preclude oversedation, dizziness and/or ataxia. If combined with other drugs having hypnotic or CNS-depressant effects, consider potential additive effects. Employ usual precautions in patients who are severely depressed, or with latent depression or suicidal tendencies. Periodic blood counts and liver and kidney function tests are advised during repeated therapy. Observe usual precautions in presence of impaired renal or hepatic function.
Adverse Reactions: Dizziness, drowsiness, lightheadedness, staggering, ataxia and falling have occurred, particularly in elderly or debilitated patients. Severe sedation, lethargy, disorientation and coma, probably indicative of drug intolerance or overdosage, have been reported. Also reported were headache, heartburn, upset stomach, nausea, vomiting, diarrhea, constipation, GI pain, nervousness, talkativeness, apprehension, irritability, weakness, palpitations, chest pains, body and joint pains and GU complaints. There have also been rare occurrences of sweating, flushes, difficulty in focusing, blurred vision, burning eyes, faintness, hypotension, shortness of breath, pruritus, skin rash, dry mouth, bitter taste, excessive salivation, anorexia, euphoria, depression, slurred speech, confusion, restlessness, hallucinations, and elevated SGOT, SGPT, total and direct bilirubins and alkaline phosphatase. Paradoxical reactions, *e.g.*, excitement, stimulation and hyperactivity, have also been reported in rare instances.
Dosage: Individualize for maximum beneficial effect. *Adults:* 30 mg usual dosage; 15 mg may suffice in some patients. *Elderly or debilitated patients:* 15 mg initially until response is determined.
Supplied: Capsules containing 15 mg or 30 mg flurazepam HCl.



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- **reduces nighttime awakenings**
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REFERENCES: 1. Kales A, *et al*: *Arch Gen Psychiatry 23*:226-232, Sep 1970
2. Karacan I, Williams RL, Smith JR: The sleep laboratory in the investigation of sleep and sleep disturbances. Scientific exhibit at the 124th annual meeting of the American Psychiatric Association, Washington DC, May 3-7, 1971
3. Frost JD Jr: Data on file, Medical Department, Hoffmann-La Roche Inc, Nutley NJ
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Indications: Based on a review of PREMARIN Tablets by the National Academy of Sciences-National Research Council and/or other information, FDA has classified the indications for use as follows:
Effective: As replacement therapy for naturally occurring or surgically induced estrogen deficiency states associated with: the climacteric, including the menopausal syndrome and postmenopause; senile vaginitis and kraurosis vulvae, with or without pruritus.
"Probably" effective: For estrogen deficiency-induced osteoporosis, and only when used in conjunction with other important therapeutic measures such as diet, calcium, physiotherapy, and good general health-promoting measures. Final classification of this indication requires further investigation.

Contraindications: Short acting estrogens are contraindicated in patients with (1) markedly impaired liver function; (2) known or suspected carcinoma of the breast, except those cases of progressing disease not amenable to surgery or irradiation occurring in women who are at least 5 years postmenopausal; (3) known or suspected estrogen-dependent neoplasia, such as carcinoma of the endometrium; (4) thromboembolic disorders, thrombophlebitis, cerebral embolism, or in patients with a past history of these conditions; (5) undiagnosed abnormal genital bleeding.
Warnings: Estrogen therapy should not be given to women with recurrent chronic mastitis or abnormal mammograms except, if in the opinion of the physician, it is warranted despite the possibility of aggravation of the mastitis or stimulation of undiagnosed estrogen-dependent neoplasia.

The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, retinal thrombosis, cerebral embolism and pulmonary embolism). If these occur or are suspected, estrogen therapy should be discontinued immediately.

Estrogens may be excreted in the mother's milk and an estrogenic effect upon the infant has been described. The long range effect on the nursing infant cannot be determined at this time.

Hypercalcemia may occur in as many as 15 percent of breast cancer patients with metastases, and this usually indicates progression of bone metastases. This occurrence depends neither on dose nor on immobilization. In the presence of progression of the cancer or hypercalcemia, estrogen administration should be stopped.

A statistically significant association has been reported between maternal ingestion of diethylstilbestrol during pregnancy and the occurrence of vaginal carcinoma in the offspring. This occurred with the use of diethylstilbestrol for the treatment of threatened abortion or high risk pregnancies. Whether or not such an association is applicable to all estrogens is not known at this time. In view of this finding, however, the use of any estrogen in pregnancy is not recommended.

Failure to control abnormal uterine bleeding or unexpected recurrence is an indication for curettage.
Precautions: As with all short acting estrogens, the following precautions should be observed:

A complete pretreatment physical examination should be performed with special reference to pelvic and breast examinations.

To avoid prolonged stimulation of the endometrium and breasts in climacteric or hypogonadal women, estrogens should be administered cyclically (3 week regimen with 1 week rest period—withdrawal bleeding may occur during rest period).

Because of individual variation in endogenous estrogen production, relative overdosage may occur which could cause undesirable effects such as abnormal or excessive uterine bleeding, mastodynia and edema.

Because of salt and water retention associated with estrogenic anabolic activity, estrogens should be used with caution in patients with epilepsy, migraine, asthma, cardiac, or renal disease.

If unexplained or excessive vaginal bleeding should occur, reexamination should be made for organic pathology.

Pre-existing uterine fibromyomata may increase in size while using estrogens; therefore, patients should be examined at regular intervals while receiving estrogenic therapy.

The pathologist should be advised of estrogen therapy when relevant specimens are submitted.

Because of their effects on epiphyseal closure, estrogens should be used judiciously in young patients in whom bone growth is incomplete.

Prolonged high dosages of estrogens will inhibit anterior pituitary functions. This should be borne in mind when treating patients in whom fertility is desired.

The age of the patient constitutes no absolute limiting factor, although treatment with estrogens may mask the onset of the climacteric.

Certain liver and endocrine function tests may be affected by exogenous estrogen administration. If test results are abnormal in a patient taking estrogen, they should be repeated after estrogen has been withdrawn for one cycle.
Adverse Reactions: The following adverse reactions have been reported associated with short acting estrogen administration:
nausea, vomiting, anorexia
gastrointestinal symptoms such as abdominal cramps and bloating
breakthrough bleeding, spotting, unusually heavy withdrawal bleeding (See DOSAGE AND ADMINISTRATION)
breast tenderness and enlargement
reactivation of endometriosis
possible diminution of lactation when given immediately postpartum
loss of libido and gynecomastia in males
edema
aggravation of migraine headaches
change in body weight (increase, decrease)
headache
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Menopausal Syndrome—1.25 mg. daily, cyclically. Adjust dosage upward or downward according to severity of symptoms and response of the patient. For maintenance, adjust dosage to lowest level that will provide effective control.

If the patient has not menstruated within the last two months or more, cyclic administration is started arbitrarily. If the patient is menstruating, cyclic administration is started on day 5 of bleeding. If breakthrough bleeding (bleeding or spotting during estrogen therapy) occurs, increase estrogen dosage as needed to stop bleeding. In the following cycle, employ the dosage level used to stop breakthrough bleeding in the previous cycle. In subsequent cycles, the estrogen dosage is gradually reduced to the lowest level which will maintain the patient symptom-free.

Postmenopause—as a protective measure against estrogen deficiency-induced degenerative changes (*e.g.* osteoporosis, atrophic vaginitis, kraurosis vulvae)—0.3 mg. to 1.25 mg. daily and cyclically. Adjust dosage to lowest effective level.

Osteoporosis (to retard progression)—usual dosage 1.25 mg. daily and cyclically.

Senile Vaginitis, Kraurosis Vulvae with or without Pruritus—0.3 mg. to 1.25 mg. or more daily, depending upon the tissue response of the individual patient. Administer cyclically.
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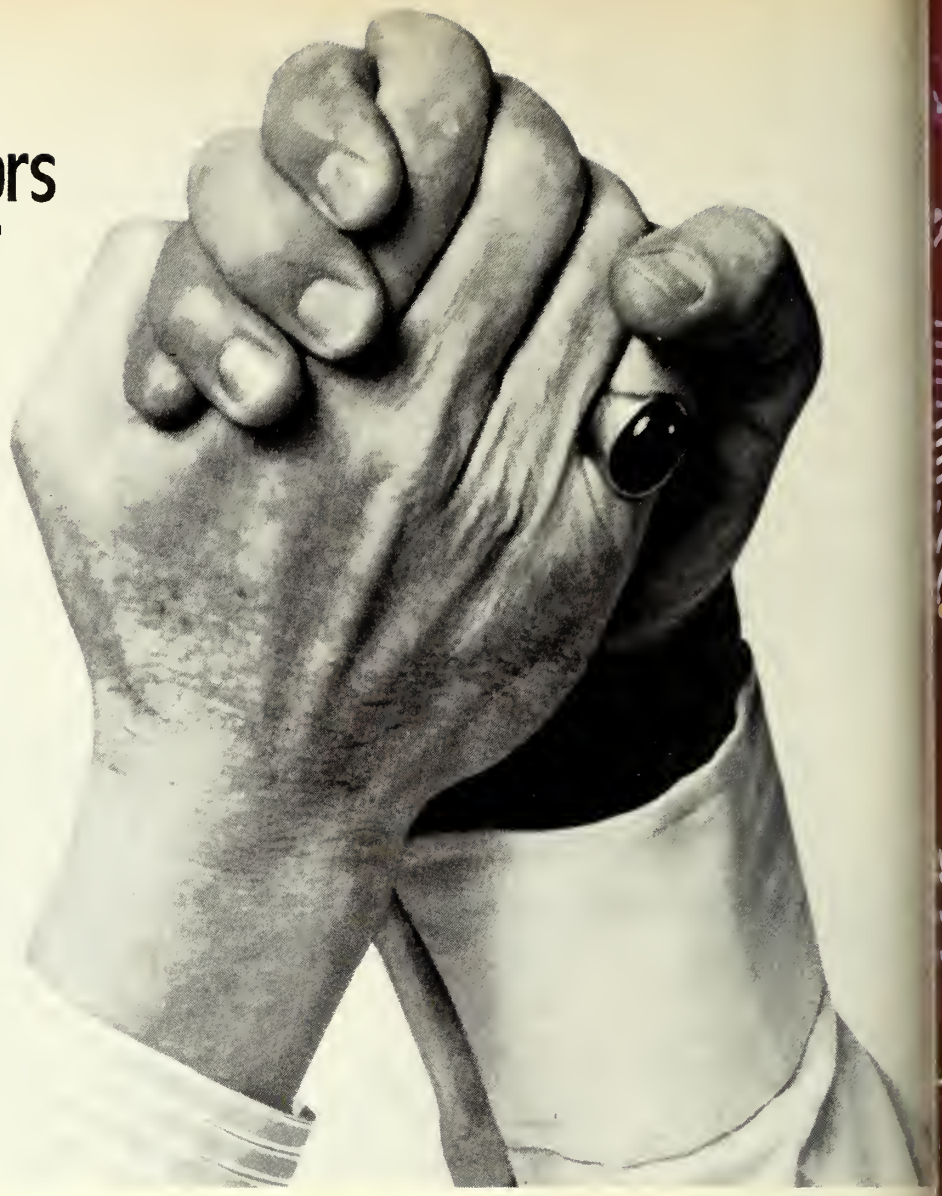

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In fact, there are no known contraindications to the use of Vasodilan in recommended oral doses, other than that it should not be given in the presence of frank arterial bleeding or immediately postpartum.

1. Gertler, M. M., et al.: Geriatrics *25*:134-148 (May) 1970.

Indications: Based on a review of this drug by the National Academy of Sciences-National Research Council and/or other information, the FDA has classified the indications as follows:

Possibly Effective:

1. For the relief of symptoms associated with cerebral vascular insufficiency.
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3. Threatened abortion.

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Composition: Vasodilan tablets, isoxsuprine HCl, 10 mg. and 20 mg.

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Adverse Reactions: On rare occasions, oral administration of the drug has been associated in time with the occurrence of severe rash. When rash appears, the drug should be discontinued. Occasional overdosage effects such as transient palpitation or dizziness are usually controlled by reducing the dose.

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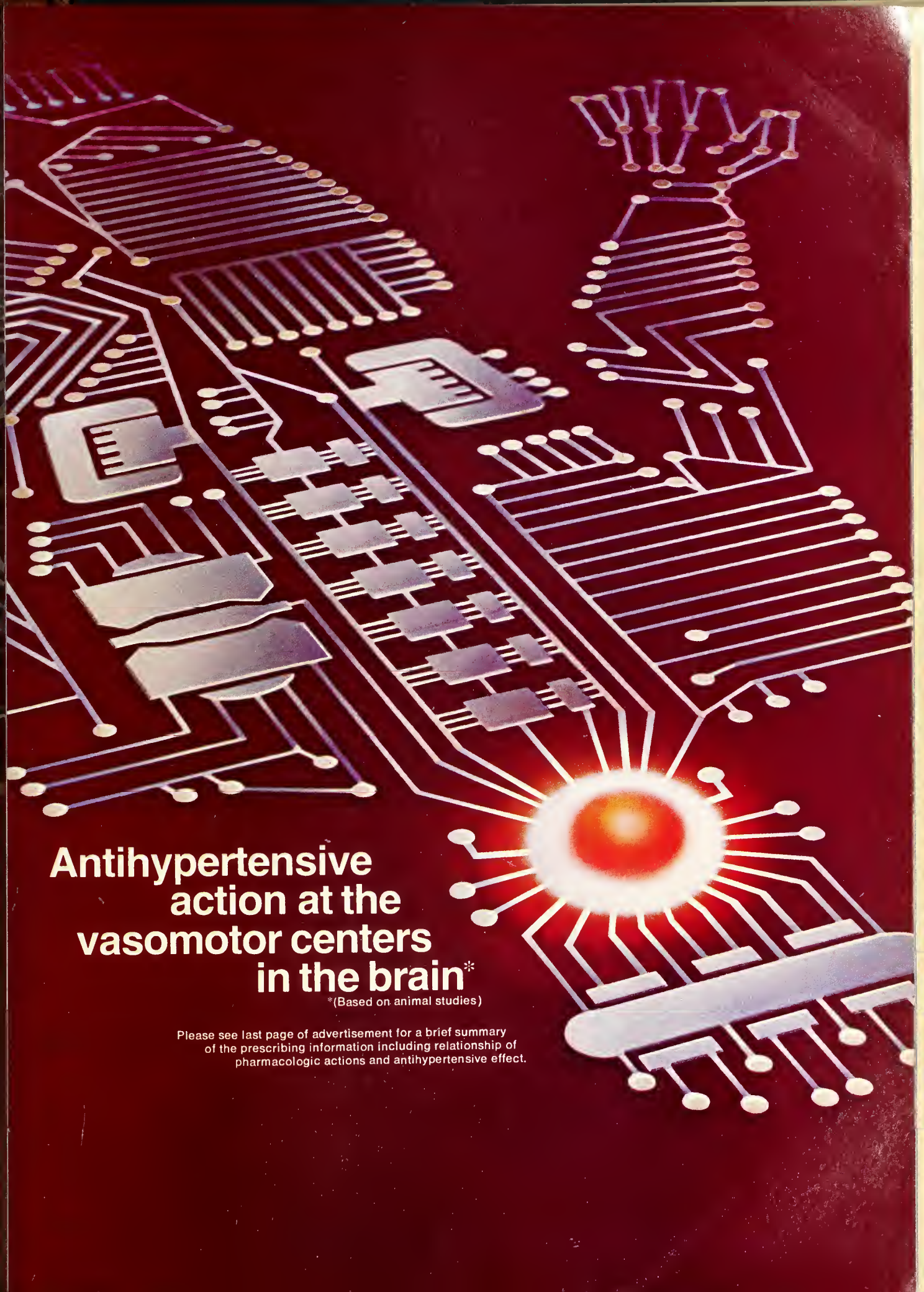
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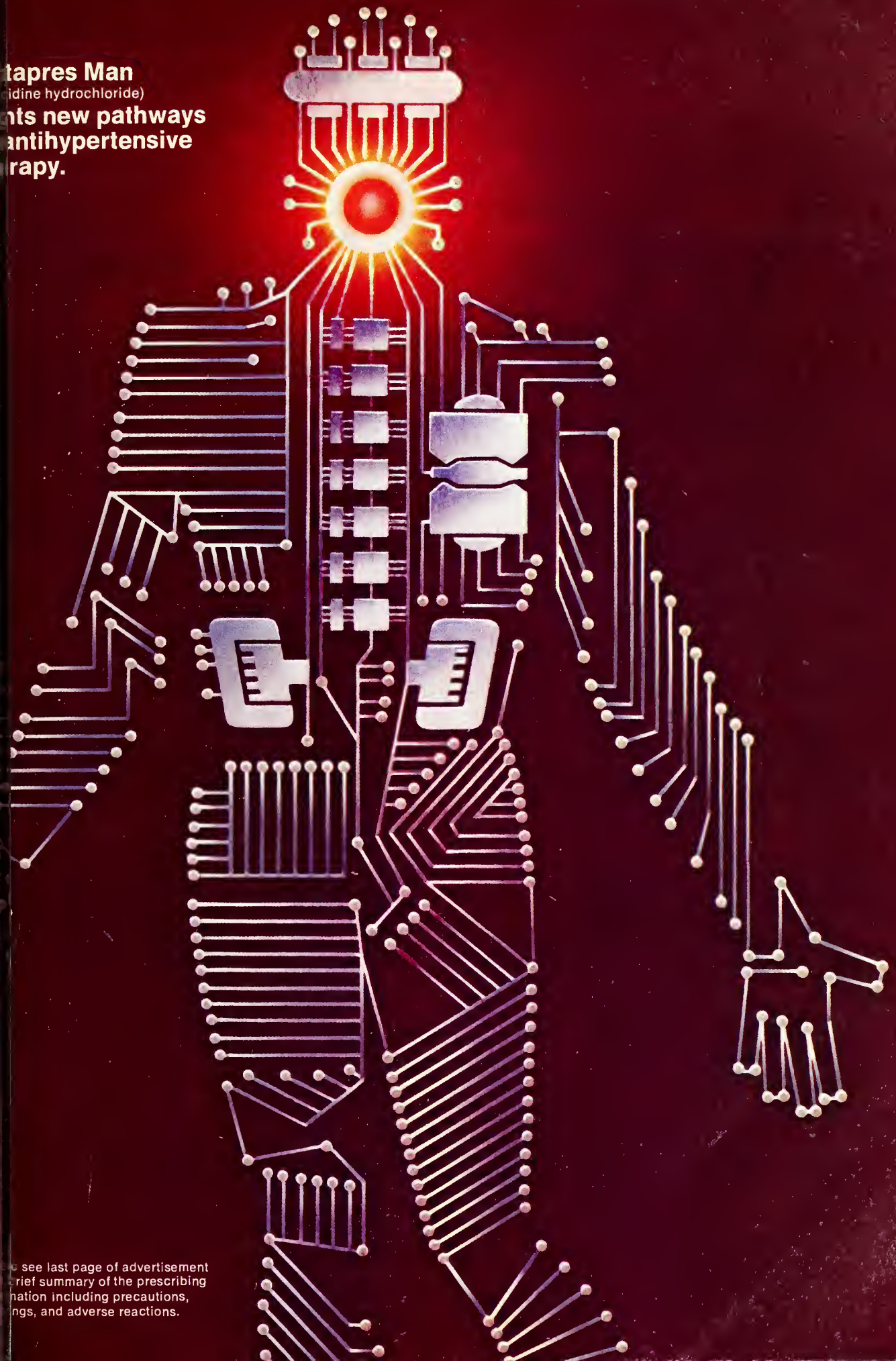
antihypertensive
rapy.



see last page of advertisement
rief summary of the prescribing
nation including precautions,
ngs, and adverse reactions.

new Catapres®
(clonidine hydrochloride)

Effective in hypertension, mild to severe

Catapres is distinguished by its broad clinical usefulness in the treatment of hypertension.

More than 600 major published papers*

The extensive experimental and clinical work with Catapres has been reported in hundreds of papers published in scientific journals in this country and abroad. Controlled studies[1-7] plus numerous other clinical evaluations have demonstrated that Catapres is an effective antihypertensive drug with these desirable properties:

does not alter normal hemodynamic responses to exercise

renal blood flow and glomerular filtration rate essentially unchanged

antihypertensive response enhanced by diuretics such as chlorthalidone

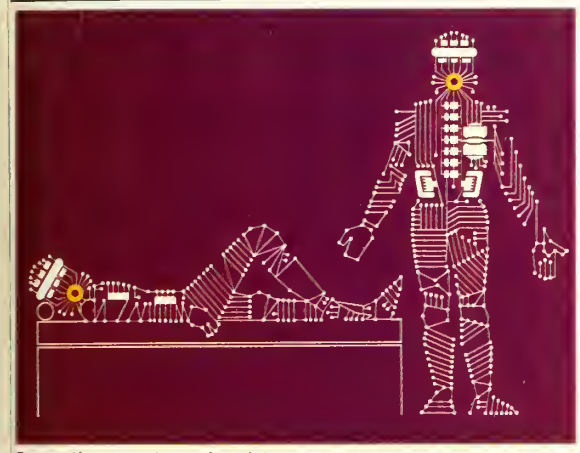
compatible with other antihypertensive agents

has been shown to reduce plasma renin activity and to decrease excretion of aldosterone and catecholamines
(See ACTIONS section of Brief Summary)

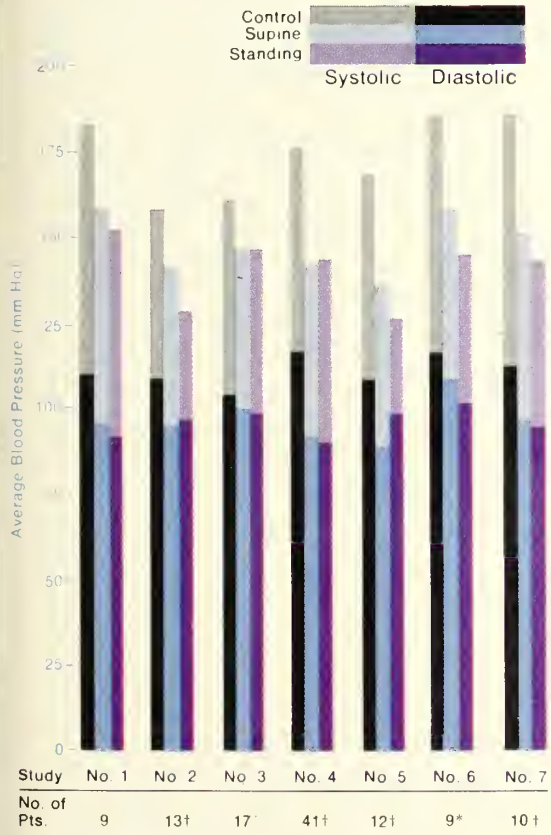
What to watch for— The principal side effects of Catapres are dry mouth, sedation, and drowsiness. Constipation, dizziness, headache, and fatigue also have been reported. Generally, these effects tend to diminish with continued therapy. As with other antihypertensive agents, tolerance may develop in some instances. For a more detailed discussion of side effects, warnings, and precautions, see the brief summary of prescribing information on the last page of this advertisement or consult the Catapres package insert.

*Complete Catapres bibliography available on request.

Mild and infrequent orthostatic effects

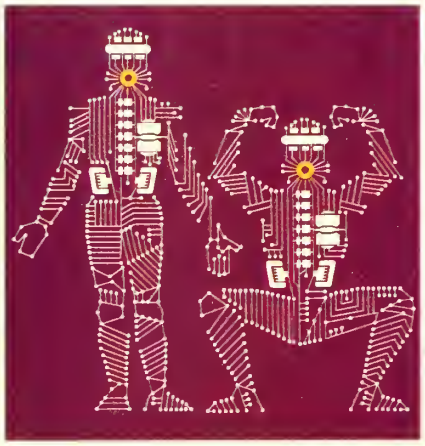


Standing and supine blood pressure response at the conclusion of therapy in 7 controlled studies[1-7]

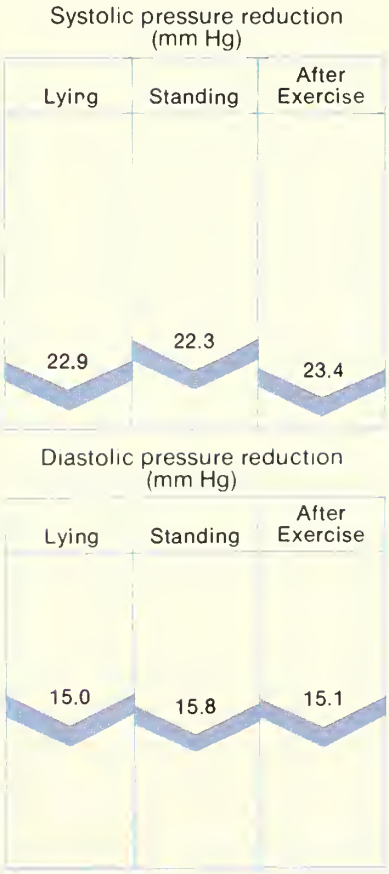


*Received Catapres alone.
†Received Catapres + a diuretic.
Note: In study No. 4, blood pressure was taken in the sitting rather than the supine position.

Normal hemodynamic responses to exercise not altered

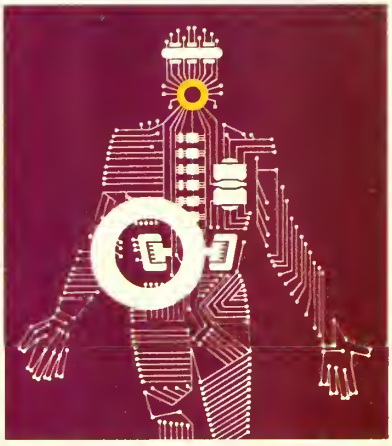


Mean blood pressure reductions in 9 hypertensive patients receiving Catapres (0.15 mg daily) for 4 weeks

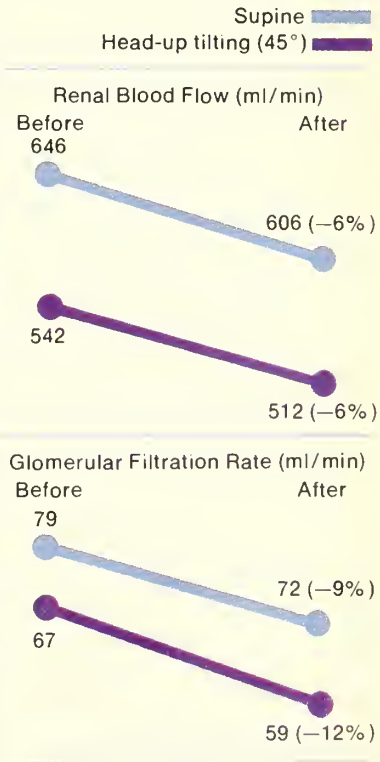


Adapted from Elkeles *et al.*[1]

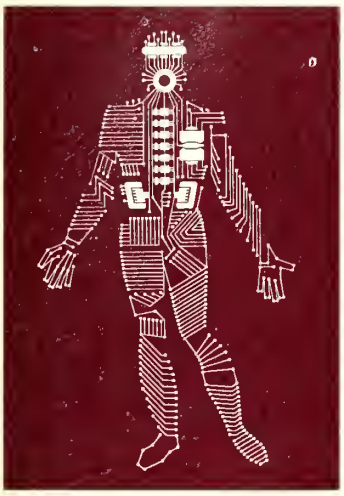
Renal blood flow and glomerular filtration rate essentially unchanged



Renal hemodynamics before and after Catapres in 7 hypertensive patients. Mean blood pressure reductions were significant in both the supine position (from 155 to 128 mm Hg) and the standing position (from 151 to 101 mm Hg).



Adapted from Onesti *et al.*[8]



new Catapres®
(clonidine hydrochloride)

It's easy to start with Catapres. The usual starting dose of Catapres is one 0.1 mg tablet twice daily. Increments of 0.1 to 0.2 mg per day (up to the maximum daily dose of 2.4 mg) may be made until the desired blood pressure response is achieved.

How to stop Catapres. Reduce the dose gradually over two to four days to avoid a possible rapid rise in blood pressure and associated subjective symptoms such as nervousness, agitation, and headache. Patients on Catapres should be instructed not to discontinue therapy without consulting their physician. It has been demonstrated that a rapid rise in blood pressure, should it occur, can be reversed by resumption of Catapres or by administration of intravenous phentolamine.

Catapres®
(clonidine hydrochloride)
Tablets of 0.1 mg and 0.2 mg

Actions: The mechanism of action appears to be central alpha-adrenergic stimulation as demonstrated in animal studies. This results in inhibition of bulbar sympathetic cardioaccelerator and sympathetic vasoconstrictor centers, thereby decreasing sympathetic outflow from the brain. Other studies in humans have provided evidence of a reduction in plasma renin activity and the excretion of aldosterone and catecholamines. The exact relationship between these pharmacologic actions of Catapres (clonidine hydrochloride) in humans and its antihypertensive effect has not been fully elucidated at this time.

Indication: The drug is indicated in the treatment of hypertension. As an antihypertensive drug, Catapres (clonidine hydrochloride) is mild to moderate in potency. It may be employed in a general treatment program with a diuretic and/or other antihypertensive agents as needed for proper patient response.

Warnings: Tolerance may develop in some patients necessitating a reevaluation of therapy.
Usage in Pregnancy: In view of embryotoxic findings in animals, and since information on possible adverse effects in pregnant women is limited to uncontrolled clinical data, the drug is not recommended in women who are or may become pregnant unless the potential benefits outweigh the potential risk to mother and fetus.
Usage in Children: No clinical experience is available with the use of Catapres (clonidine hydrochloride) in children.

Precautions: When discontinuing Catapres (clonidine hydrochloride), reduce the dose gradually over 2 to 4 days to avoid a possible rapid rise in blood pressure and associated subjective symptoms such as nervousness, agitation, and headache. Patients should be instructed not to discontinue therapy without consulting their physician. Rare instances of hypertensive encephalopathy and death have been recorded after cessation of clonidine hydrochloride therapy. A causal relationship has not been established in these cases. It has been demonstrated that an excessive rise in blood pressure, should it occur, can be reversed by resumption of clonidine hydrochloride therapy or by intravenous phentolamine. Patients who engage in potentially hazardous activities, such as operating machinery or driving, should be advised of the sedative effect. This drug may enhance the CNS-depressive effects of alcohol, barbiturates and other sedatives. Like any other agent lowering blood pressure, clonidine hydrochloride should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease or chronic renal failure.

As an integral part of their overall long-term care, patients treated with Catapres (clonidine hydrochloride) should receive periodic eye examinations. While, except for some dryness of the eyes, no drug-related abnormal ophthalmologic findings have been recorded with Catapres (clonidine hydrochloride), in several studies the drug produced a dose-dependent increase in the incidence and severity of spontaneously occurring retinal degeneration in albino rats treated for 6 months or longer.

Adverse Reactions: The most common reactions are dry mouth, drowsiness and sedation. Constipation, dizziness, headache, and fatigue have been reported. Generally these effects tend to diminish with continued therapy. The following reactions have been associated with the drug, some of them rarely. (In some instances an exact causal relationship has not been established.) These include: Anorexia, malaise, nausea, vomiting, parotid pain, mild transient abnormalities in liver function tests; one report of possible drug-induced hepatitis without icterus and hyperbilirubinemia in a patient receiving clonidine hydrochloride, chlorthalidone, and papaverine hydrochloride. Weight gain, transient elevation of blood glucose, or serum creatine phosphokinase; congestive heart failure, Raynaud's phenomenon; vivid dreams or nightmares, insomnia, other behavioral changes, nervousness, restlessness, anxiety and mental depression. Also rash, angioneurotic edema, hives, urticaria, thinning of the hair, pruritus not associated with a rash, impotence, urinary retention, increased sensitivity to alcohol, dryness, itching or burning of the eyes, dryness of the nasal mucosa, pallor, gynecomastia, weakly positive Coombs' test, asymptomatic electrocardiographic abnormalities manifested as Wenckebach period or ventricular trigeminy.

Overdosage: Profound hypotension, weakness, somnolence, diminished or absent reflexes and vomiting followed the accidental ingestion of Catapres (clonidine hydrochloride) by several children from 19 months to 5 years of age. Gastric lavage and administration of an analeptic and vasopressor led to complete recovery within 24 hours. Tolazoline in intravenous doses of 10 mg at 30-minute intervals usually abolishes all effects of Catapres (clonidine hydrochloride) overdosage.

How Supplied: Catapres, brand of clonidine hydrochloride, is available as 0.1 mg (tan) and 0.2 mg (orange) oval, single-scored tablets in bottles of 100.

For complete details, please see full prescribing information.

Under license from Boehringer Ingelheim GmbH

References: 1. Elkeles, R. S., Goldby, F. S. and Oliver, D. O.: A Double Blind Study of Catapres, A New Hypotensive Agent, *in* Conolly, M. E. (ed.): Catapres in Hypertension, London, Butterworths, 1970, pp. 139-144. 2. Freis, E. D.: Data on file at Boehringer Ingelheim Ltd. 3. Hickler, R. B.: Data on file at Boehringer Ingelheim Ltd. 4. Mroczek, W. J., Leibel, B. A. and Finnerty, F. A., Jr.: Comparison of clonidine and methyldopa in hypertensive patients receiving a diuretic, Am. J. Cardiol. **29**:712, 1972. 5. Putzeys, M. R. and Hoobler, S. W.: Comparison of clonidine and methyldopa on blood pressure and side effects in hypertensive patients, Am. Heart J. **83**:464, 1972. 6. MacDonald, R. H. and Shapiro, A.: Data on file at Boehringer Ingelheim Ltd. 7. Kirkendall, W. M., Toubes, D. B. *et al.*: Hypertensive effects of clonidine and chlorthalidone, Am. Heart J. **82**:312, 1971. 8. Onesti, G. *et al.*: Pharmacodynamic effects of a new antihypertensive drug, Catapres (ST-155), Circulation **39**:219, 1969.

Boehringer Ingelheim
Boehringer Ingelheim Ltd.
Elmsford, New York 10523

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PHYSICIANS WANTED

FRESNO COUNTY has immediate opening for Senior Public Health Physician position to direct public health programs. Exciting new comprehensive Department of Health concept including opportunity to participate in Environmental Health and Outreach Program development. Salary: $39,000-$43,000. Located in the heart of the San Joaquin Valley with easy access to the mountains, ocean, Los Angeles area or San Francisco area. Contact: Trevor D. Glenn, MD, Director, Department of Health, 515 South Cedar, Fresno, CA 93702. Phone: (209) 488-3743.

SANTA BARBARA—Family Practice physician for full-time staff position at County-operated teaching hospital. Salary to $34,088 ($35,831 if Board Certified) plus fringes. CONTACT: Edgar Rosen, MD, Med. Dir., Santa Barbara General Hospital, P.O. Box 3650, Santa Barbara, CA 93105. Phone: (805) 967-2311.

SANTA BARBARA—Internist, Board Certified, full-time staff position as Clinical Director of Medicine, at County-operated teaching hospital. Salary $35,831 plus fringes. CONTACT: Edgar Rosen, MD, Med. Dir., Santa Barbara General Hospital, P.O. Box 3650, Santa Barbara, CA 93105. Phone: (805) 967-2311.

COLLEGE TOWN on California's North Coast, in heart of the redwoods. Multi-specialty group has openings for 3 Residency-trained Family Practitioners, Ob-Gyn and Pediatricians for Summer '75. Salary first 6 months with partnership later. Building new clinic next to 2-year-old hospital. Write or call Dan A. Andrews, MD, 3798 Janes Rd., Arcata, CA (707) 822-6644.

SACRAMENTO, CALIFORNIA, City of 650,000 has excellent opportunities for all specialties, especially general practitioners and internal medicine. Smog free, no snow, one hour to Lake Tahoe and mountain ski resorts, one and one-half hours to San Francisco. Excellent hunting and fishing, State Capitol, University of California Medical School. New, growing hospital with Medical Office Building immediately adjacent. Inquire: Stanley C. Oppegard, Administrator, Methodist Hospital of Sacramento, 7500 Timberlake Way, Sacramento, CA 95823. Tel. (916) 391-7440.

CLINICAL CARDIOLOGY

A Fellowship is offered in Clinical Cardiology at Huntington Memorial Hospital. Excellent experience in all phases of clinical cardiology. Invasive and non-invasive techniques are under the supervision of a full-time Director of Cardiology. Experience is offered in both adult and pediatric cardiology. Active on-going cardiac surgery program. Direct inquiries to David A. Swan, MD, FACC, Huntington Memorial Hospital, 100 Congress St., Pasadena, CA 91105.

PHYSICIANS WANTED

CARDIOLOGIST—Board certified internist with subspecialty in cardiology needed for busy cardiology practice in Orange County, with excellent facilities and adjacent medical school. Send résumé to Box 9392, Western Journal of Medicine, 731 Market St., San Francisco, 94103.

FULL-TIME EMERGENCY CARE position with pre-payment group. Includes both hospital and clinic emergency care work. Partnership after two years. Excellent insurance and retirement programs. Robert A. McFarlane, MD, 5055 North Greeley Ave., Portland, Ore. 97217.

STEINBECK COUNTRY: Innovative, progressive rural group practice located in the Salinas Valley has an immediate need for 2 Family Practitioners, a Pediatrician and an Internist with broad-based capabilities. In addition to 9 full-time physicians, the group has 11 consultants, representing a wide spectrum of the specialties, visiting on a routine basis. University affiliation with on-site teaching. Top fringe benefits, including competitive starting salary (1st year minimum of $34,000 guaranteed), and early affiliation. Brochure by return mail. Please call or send C.V. to: Duane F. Hyde, MD, Southern Monterey County Medical Group (A Professional Corporation), 210 Canal Street, King City, CA 93930; (408) 385-5471.

PULMONARY DISEASE PHYSICIAN, certified, to associate with a Cardiologist in Orange County. Send curriculum vitae to: E. C. Gaulden, MD, 17541 Irvine Blvd., Tustin, CA, or call (714) 838-2655.

ORTHOPEDIST: Board certified or board eligible, for large multispecialty group. Department currently consists of seven orthopedists. Department and area expanding. Edward H. Start, MD, Chief of Orthopedics, The Permanente Clinic, 5055 North Greeley Ave., Portland, Oregon 97217.

SAN LUIS OBISPO, CALIFORNIA—Openings for full time psychiatrists at the California Men's Colony in a newly evolving and expanding treatment program for young adult felons. Salary to $39,792. Located in California's finest weather and sportsman's paradise, including a wide variety of recreation, such as golfing, hunting, fresh water and ocean fishing. Contact C. L. Pickett, MD, Assistant Superintendent, Psychiatric Services, California Men's Colony, San Luis Obispo, CA 93409, or call collect (805) 543-2700.

SACRAMENTO, CALIFORNIA: Position of Chief of Professional Services at Mercy General Hospital. Responsible for fostering, organizing and administering a meaningful education program for the medical staff; working with audit committees in problem oriented records; medical liaison with in-service training of nursing and other ancillary personnel; will have administrative functions and be a member of and responsible to the Medical Executive Committee. The hospital soon will have an affiliation with the University of California at Davis. Mercy has 364 licensed beds and a medical staff of 600 doctors. Applicants must have experience in the field of Medical Education; Specialty Board Certification is desired. Salary in the range of $42,000 per annum—negotiable depending upon qualifications. CONTACT: Donald G. Dresel, Administrator, Mercy Hospital, 4001 J Street, Sacramento, CA 95819.

ORANGE COUNTY: Very rapidly expanding HMO requires more GP's/FP's, Internists and Pediatricians. Positions available immediately. Starting salary range $50,000 with increases. Immediate profit sharing. Partnership after one year, no investment required. Outstanding fringe benefits. Contact: Neil Hollander, MD, Chapman Health Center, 1937 West Chapman Ave., Orange, CA 92668. Call: (714) 997-9550.

ONCOLOGY FELLOWSHIP IN SURGICAL PATHOLOGY including electron microscopy available at LAC-USC Medical Center for one year starting July 1, 1975. Applicants must be citizens of the U.S.A. and eligible for licensure in the State of California. Previous experience in Surgical Pathology required. Please call or send C.V. to: Diane Crocker, MD, Professor of Pathology, 1200 N. State St., Los Angeles, CA 90033. Phone (213) 226-4612.

(Continued on Page 34)

PHYSICIANS NEEDED

400 bed hospital undergoing rapid expansion in in-patient and out-patient programs has immediate openings for Physicians, particularly Internists, Family Physicians and Pediatricians.

Salary range: $26,736 to $36,960 per year for 40 hour week. Salaries may be increased up to 50 percent by 20 hours per week overtime. Liberal fringe benefits including malpractice insurance.

Contact E. J. Carmody, MD, Medical Director

LONG BEACH GENERAL HOSPITAL

2597 Redondo Avenue
Long Beach, CA 90806
(213) 427-9951

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820 West Compton Boulevard
COMPTON, CALIFORNIA 90220
(213) 537-3070
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and
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High Standards of Psychiatric Treatment . . . Serving the Los Angeles Area

Accredited by Joint Commission on Accreditation of Hospitals

When diarrhea has his number...

Lomotil puts him back in the game.

Physicians and patients both want prompt control of the symptoms of diarrhea. A rapid, uncontrolled loss of fluids and electrolytes can cause a medical crisis, particularly in children, and in patients who are seriously ill, or in people who are badly undernourished.

Lomotil usually stops diarrhea promptly. This rapid action halts the emergency aspect of diarrhea and is comforting and reassuring to the patient. Electrolyte and fluid losses can be corrected while the specific cause of the diarrhea is being determined. If an infective agent is the cause, appropriate antibiotic therapy should be given along with Lomotil.

Lomotil has few side effects, and those that do occur are generally mild.

Lomotil®
TABLETS/LIQUID

Each tablet and each 5 ml. of liquid contain:
diphenoxylate hydrochloride ..... 2.5 mg.
(Warning: May be habit forming)
atropine sulfate ..... 0.025 mg.

Usually stops diarrhea promptly.

IMPORTANT INFORMATION: *This is a Schedule V substance by Federal law; diphenoxylate HCl is chemically related to meperidine. In case of overdosage or individual hypersensitivity, reactions similar to those after meperidine or morphine overdosage may occur; treatment is similar to that for meperidine or morphine intoxication (prolonged and careful monitoring). Respiratory depression may recur in spite of an initial response to Nalline® (nalorphine HCl) or may be evidenced as late as 30 hours after ingestion. LOMOTIL IS NOT AN INNOCUOUS DRUG AND DOSAGE RECOMMENDATIONS SHOULD BE STRICTLY ADHERED TO, ESPECIALLY IN CHILDREN. THIS MEDICATION SHOULD BE KEPT OUT OF REACH OF CHILDREN.*

Indications: Lomotil is effective as adjunctive therapy in the management of diarrhea.

Contraindications: In children less than 2 years, due to the decreased safety margin in younger age groups, and in patients who are jaundiced or hypersensitive to diphenoxylate HCl or atropine.

Warnings: Use with caution in young children, because of variable response, and with extreme caution in patients with cirrhosis and other advanced hepatic disease or abnormal liver function tests, because of possible hepatic coma. Diphenoxylate HCl may potentiate the action of barbiturates, tranquilizers and alcohol. In theory, the concurrent use with monoamine oxidase inhibitors could precipitate hypertensive crisis.

Usage in pregnancy: Weigh the potential benefits against possible risks before using during pregnancy, lactation or in women of childbearing age. Diphenoxylate HCl and atropine are secreted in the breast milk of nursing mothers.

Precautions: Addiction (dependency) to diphenoxylate HCl is theoretically possible at high dosage. Do not exceed recommended dosages. Administer with caution to patients receiving addicting drugs or known to be addiction prone or having a history of drug abuse. The subtherapeutic amount of atropine is added to discourage deliberate overdosage; strictly observe contraindications, warnings and precautions for atropine; use with caution in children since signs of atropinism may occur even with the recommended dosage.

Adverse reactions: Atropine effects include dryness of skin and mucous membranes, flushing and urinary retention. Other side effects with Lomotil include nausea, sedation, vomiting, swelling of the gums, abdominal discomfort, respiratory depression, numbness of the extremities, headache, dizziness, depression, malaise, drowsiness, coma, lethargy, anorexia, restlessness, euphoria, pruritus, angioneurotic edema, giant urticaria and paralytic ileus.

Dosage and administration: ***Lomotil is contraindicated in children less than 2 years old.*** Use only Lomotil liquid for children 2 to 12 years old. For ages 2 to 5 years, 4 ml. (2 mg.) t.i.d.; 5 to 8 years, 4 ml. (2 mg.) q.i.d.; 8 to 12 years, 4 ml. (2 mg.) 5 times daily; adults, two tablets (5 mg.) t.i.d. to two tablets (5 mg.) q.i.d. or two regular teaspoonfuls (10 ml., 5 mg.) q.i.d. Maintenance dosage may be as low as one fourth of the initial dosage. Make downward dosage adjustment as soon as initial symptoms are controlled.

Overdosage: Keep the medication out of the reach of children since accidental overdosage may cause severe, even fatal, respiratory depression. Signs of overdosage include flushing, lethargy or coma, hypotonic reflexes, nystagmus, pinpoint pupils, tachycardia and respiratory depression which may occur 12 to 30 hours after overdose. Evacuate stomach by lavage, establish a patent airway and, when necessary, assist respiration mechanically. Use a narcotic antagonist in severe respiratory depression. Observation should extend over at least 48 hours.

Dosage forms: Tablets, 2.5 mg. of diphenoxylate HCl with 0.025 mg. of atropine sulfate. *Liquid,* 2.5 mg. of diphenoxylate HCl and 0.025 mg. of atropine sulfate per 5 ml. A plastic dropper calibrated in increments of ½ ml. (total capacity, 2 ml.) accompanies each 2-oz. bottle of Lomotil liquid.

SEARLE **Searle & Co.**
San Juan, Puerto Rico 00936

Address medical inquiries to:
G. D. Searle & Co.
Medical Department, Box 5110,
Chicago, Illinois 60680

454 R

The Pain Phone

When a telephone prescription for pain relief is necessary or convenient, you can call in your order for Empirin Compound with Codeine in 45 of the 50 states† That includes No. 4, which provides a full grain of codeine for more intense, acute pain.

† The exceptions: Alaska, Arizona, Maine, Oregon, Rhode Island, and the District of Columbia.

EMPIRIN® COMPOUND c̄ CODEINE

No. 4 codeine phosphate* (64.8 mg) gr 1

No. 3 codeine phosphate* (32.4 mg) gr ½

Each tablet also contains aspirin gr 3½, phenacetin gr 2½, caffeine gr ½.

*Warning—may be habit-forming.

CIII

Wellcome | **Burroughs Wellcome Co.**
Research Triangle Park
North Carolina 27709

Before prescribing, see complete prescribing information in SK&F literature or *PDR*. The following is a brief summary.

Indications: Edema associated with congestive heart failure, cirrhosis of the liver, the nephrotic syndrome; steroid-induced and idiopathic edema; edema resistant to other diuretic therapy. Also, mild to moderate hypertension.

Contraindications: Pre-existing elevated serum potassium. Hypersensitivity to either component. Continued use in progressive renal or hepatic dysfunction or developing hyperkalemia.

Warnings: **Do not use dietary potassium supplements or potassium salts unless hypokalemia develops or dietary potassium intake is markedly impaired.** Enteric-coated potassium salts may cause small bowel stenosis with or without ulceration. Hyperkalemia (>5.4 mEq/L) has been reported in 4% of patients under 60 years, in 12% of patients over 60 years, and in less than 8% of patients overall. Rarely, cases have been associated with cardiac irregularities. Accordingly, **check serum potassium during therapy, particularly in patients with suspected or confirmed renal insufficiency (e.g., elderly or diabetics). If hyperkalemia develops, substitute a thiazide alone. If spironolactone is used concomitantly with 'Dyazide', check serum potassium frequently**—both can cause potassium retention and sometimes hyperkalemia. Two deaths have been reported in patients on such combined therapy (in one, recommended dosage was exceeded; in the other, serum electrolytes were not properly monitored). Observe patients on 'Dyazide' regularly for possible blood dyscrasias, liver damage or other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving Dyrenium (triamterene, SK&F). Rarely, leukopenia, thrombocytopenia, agranulocytosis, and aplastic anemia have been reported with the thiazides. Watch for signs of impending coma in acutely ill cirrhotics. Thiazides are reported to cross the placental barrier and appear in breast milk. This may result in fetal or neonatal hyperbilirubinemia, thrombocytopenia, altered carbohydrate metabolism and possibly other adverse reactions that have occurred in the adult. When used during pregnancy or in women who might bear children, weigh potential benefits against possible hazards to fetus.

Precautions: Do periodic serum electrolyte and BUN determinations. Do periodic hematologic studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in post-sympathectomy patients. The following may occur: hyperuricemia and gout, reversible nitrogen retention, decreasing alkali reserve with possible metabolic acidosis, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), digitalis intoxication (in hypokalemia). Use cautiously in surgical patients. Concomitant use with antihypertensive agents may result in an additive hypotensive effect.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis; rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting (may indicate electrolyte imbalance), diarrhea, constipation, other gastrointestinal disturbances. Rarely, necrotizing vasculitis, paresthesias, icterus, pancreatitis, and xanthopsia have occurred with thiazides alone.

Supplied: Bottles of 100 capsules; in Single Unit Packages of 100 (intended for institutional use only).

SK&F CO.
Carolina, P.R. 00630
Subsidiary of
SmithKline Corporation

KEEP THE HYPERTENSIVE PATIENT ON THERAPY KEEP THERAPY SIMPLE WITH

DYAZIDE®

Trademark

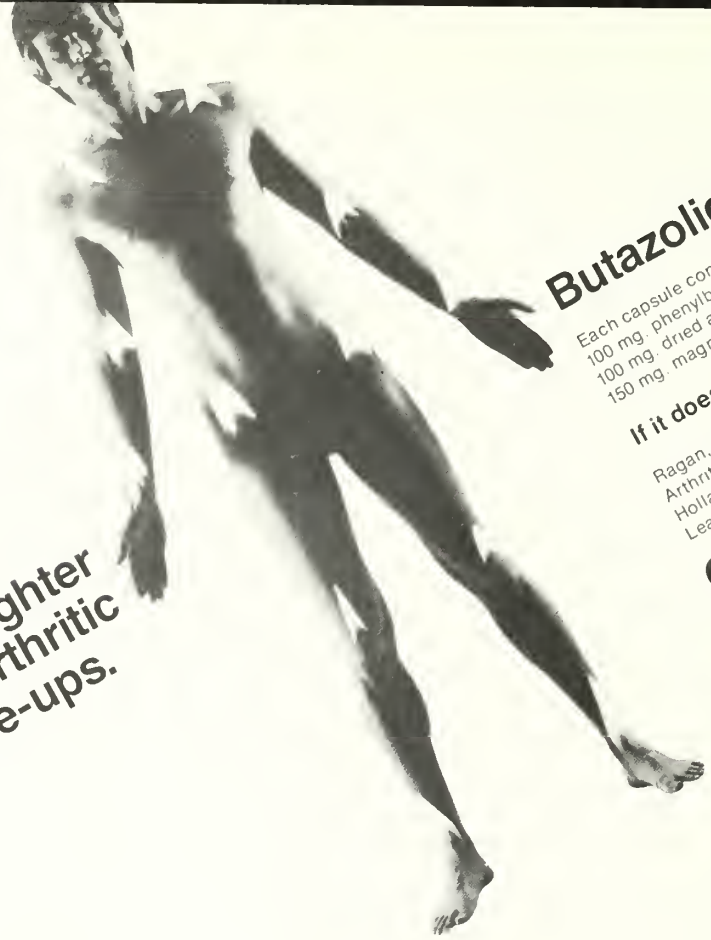
Each capsule contains 50 mg. of Dyrenium® (brand of triamterene) and 25 mg. of hydrochlorothiazide.

Just 'Dyazide' once daily or twice daily
No inconvenient potassium supplements
Nor special K^+ rich diets needed as a rule

Two prime reasons patients drop out of hypertensive therapy are (1) the patient failed to understand directions, and (2) the regimen was overly complicated. Dosage is simple with 'Dyazide', easily understood, once or twice daily, depending on response. There's no need to complicate the regimen with potassium supplements or unwieldy potassium-rich diets.

TO KEEP BLOOD PRESSURE DOWN AND KEEP POTASSIUM LEVELS UP

Putting out the fires of arthritic pain
Rheumatoid arthritis can sometimes spread like wildfire, with joint after joint going up inflamed: "The usual onset is manifested by spotty joint involvement but an acute onset of symmetrical polyarthritis may be noted."*
If aspirin fails, consider Butazolidin alka. Giving one capsule four times a day often provides prompt, pain-relieving, anti-inflammatory action to help restore joint mobility. The results you can get within a week can be maintained on as little as one or two capsules daily.
Serious side effects can occur. Select patients carefully (particularly the elderly) and follow them closely in line with the drug's precautions, warnings, contraindications and adverse reactions. For full details, please read the prescribing information. It's summarized on the back of this page.
Butazolidin® alka
Each capsule contains:
100 mg. phenylbutazone USP
100 mg. dried aluminum hydroxide gel USP
150 mg. magnesium trisilicate USP
If it doesn't work in a week, forget it.



Butazolidin® alka

Each capsule contains:
100 mg. phenylbutazone USP
100 mg. dried aluminum hydroxide gel USP
150 mg. magnesium trisilicate USP

If it doesn't work in a week, forget it.

Ragan, C. The Clinical Picture of Rheumatoid Arthritis, in Arthritis, ed. 8, edited by J. L. Hollander and D. J. McCarty, Jr., Philadelphia, Lea & Febiger, 1972, chap. 21, p. 335.

Geigy

Fire fighter for arthritic flare-ups.

Important Note This drug is not a simple analgesic. Do not administer casually. Carefully evaluate patients before starting treatment and keep them under close supervision. Obtain a detailed history, and complete physical and laboratory examination (complete hemogram, urinalysis, etc.) before prescribing and at frequent intervals thereafter. Carefully select patients, avoiding those responsive to routine measures, contraindicated patients or those who cannot be observed frequently. Warn patients not to exceed recommended dosage. Short-term relief of severe symptoms with the smallest possible dosage is the goal of therapy. Dosage should be taken with meals or a full glass of milk. Substitute alka capsules for tablets if dyspeptic symptoms occur. Patients should discontinue the drug and report immediately any sign of: fever, sore throat, oral lesions (symptoms of blood dyscrasia), dyspepsia, epigastric pain, symptoms of anemia, black or tarry stools or other evidence of intestinal ulceration or hemorrhage, skin reactions, significant weight gain or edema. A one-week trial period is adequate. Discontinue in the absence of a favorable response. Restrict treatment periods to one week in patients over sixty.

Indications Rheumatoid arthritis, osteoarthritis, bursitis, acute gouty arthritis and rheumatoid spondylitis.

Contraindications Children 14 years or less, senile patients, history or symptoms of G.I. inflammation or ulceration including severe, recurrent or persistent dyspepsia, history or presence of drug allergy, blood dyscrasias, renal, hepatic or cardiac dysfunction, hypertension, thyroid disease, systemic edema, stomatitis and salivary gland enlargement due to the drug, polymyalgia rheumatica and temporal arteritis, patients receiving other potent chemotherapeutic agents, or long-term anticoagulant therapy.

Warnings Age, weight, dosage, duration of therapy, existance of concomitant diseases, and concurrent potent chemotherapy affect incidence of toxic reactions. Carefully instruct and observe the individual patient, especially the aging (forty years and over) who have increased susceptibility to the toxicity of the drug. Use lowest effective dosage. Weigh initially unpredictable benefits against potential risk of severe, even fatal, reactions. The disease condition itself is unaltered by the drug. Use with caution in first trimester of pregnancy and in nursing mothers. Drug may appear in cord blood and breast milk. Serious, even fatal, blood dyscrasias, including aplastic anemia, may occur suddenly despite regular hemograms, and may become manifest days or weeks after cessation of drug. Any significant change in total white count, relative decrease in granulocytes, appearance of immature forms, or fall in hematocrit should signal immediate cessation of therapy and complete hematologic investigation. Unexplained bleeding involving CNS, adrenals, and G.I. tract has occurred. The drug may potentiate action of insulin, sulfonylurea, and sulfonamide-type agents. Carefully observe patients taking these agents. Nontoxic and toxic goiters and myxedema have been reported (the drug reduces iodine uptake by the thyroid). Blurred vision can be a significant toxic symptom worthy of a complete ophthalmological examination. Swelling of ankles or face in patients under sixty may be prevented by reducing dosage. If edema occurs in patients over sixty, discontinue drug.

Precautions The following should be accomplished at regular intervals. Careful detailed history for disease being treated and detection of earliest signs of adverse reactions, complete physical examination including check of patient's weight, complete weekly (especially for the aging) or an every two week blood check, pertinent laboratory studies. Caution patients about participating in activity requiring alertness and coordination, as driving a car, etc. Cases of leukemia have been reported in patients with a history of short- and long-term therapy. The majority of these patients were over forty. Remember that arthritic-type pains can be the presenting symptom of leukemia.

Adverse Reactions This is a potent drug, its misuse can lead to serious results. Review detailed information before beginning therapy. Ulcerative esophagitis, acute and reactivated gastric and duodenal ulcer with perforation and hemorrhage, ulceration and perforation of large bowel, occult G.I. bleeding with anemia, gastritis, epigastric pain, hematemesis, dyspepsia, nausea, vomiting and diarrhea, abdominal distention, agranulocytosis, aplastic anemia, hemolytic anemia, anemia due to blood loss including occult G.I. bleeding, thrombocytopenia, pancytopenia, leukemia, leukopenia, bone marrow depression, sodium and chloride retention, water retention and edema, plasma dilution, respiratory alkalosis, metabolic acidosis, fatal and nonfatal hepatitis (cholestasis may or may not be prominent), petechiae, purpura without thrombocytopenia, toxic pruritus, erythema nodosum, erythema multiforme, Stevens-Johnson syndrome, Lyell's syndrome (toxic necrotizing epidermolysis), exfoliative dermatitis, serum sickness, hypersensitivity angiitis (polyarteritis), anaphylactic shock, urticaria, arthralgia, fever, rashes (all allergic reactions require prompt and permanent withdrawal of the drug), proteinuria, hematuria, oliguria, anuria, renal failure with azotemia, glomerulonephritis, acute tubular necrosis, nephrotic syndrome, bilateral renal cortical necrosis, renal stones, ureteral obstruction with uric acid crystals due to uricosuric action of drug, impaired renal function, cardiac decompensation, hypertension, pericarditis, diffuse interstitial myocarditis with muscle necrosis, perivascular granulomata, aggravation of temporal arteritis in patients with polymyalgia rheumatica, optic neuritis, blurred vision, retinal hemorrhage, toxic amblyopia, retinal detachment, hearing loss, hyperglycemia, thyroid hyperplasia, toxic goiter, association of hyperthyroidism and hypothyroidism (causal relationship not established), agitation, confusional states, lethargy, CNS reactions associated with overdosage, including convulsions, euphoria, psychosis, depression, headaches, hallucinations, giddiness, vertigo, coma, hyperventilation, insomnia, ulcerative stomatitis, salivary gland enlargement.

(B)98-146-070-J (10/71)

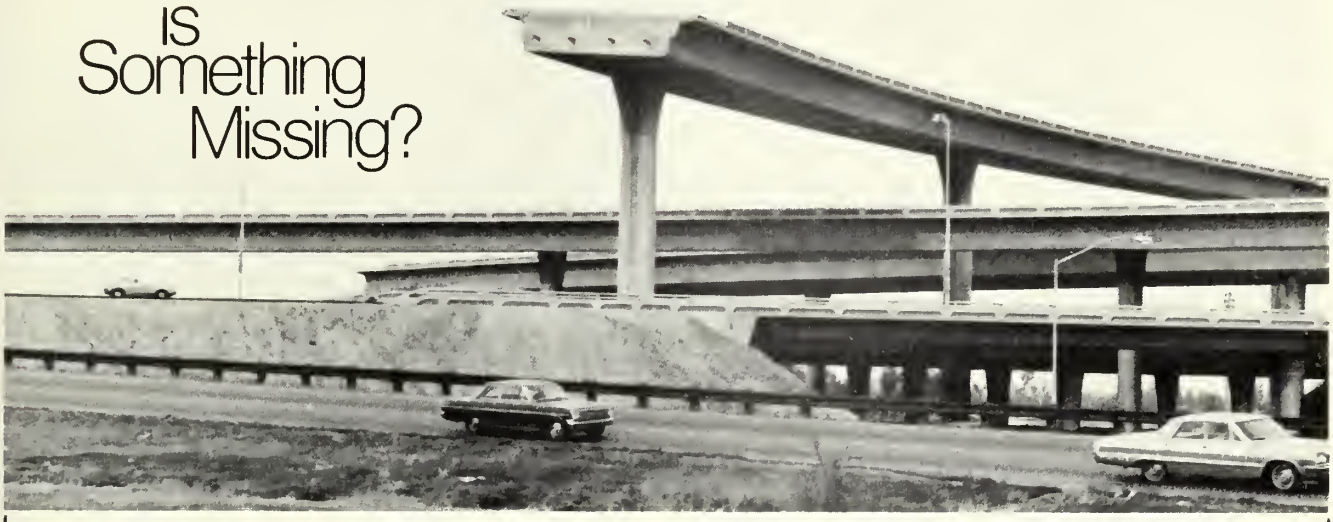
For complete details, including dosage, please see full prescribing information

GEIGY Pharmaceuticals
Division of CIBA-GEIGY Corporation
Ardsley, New York 10502

BU 10259

In the fast pace of today's medical practice...

is Something Missing?



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NAME_____ (& Degree) TYPE OF PRACTICE_____

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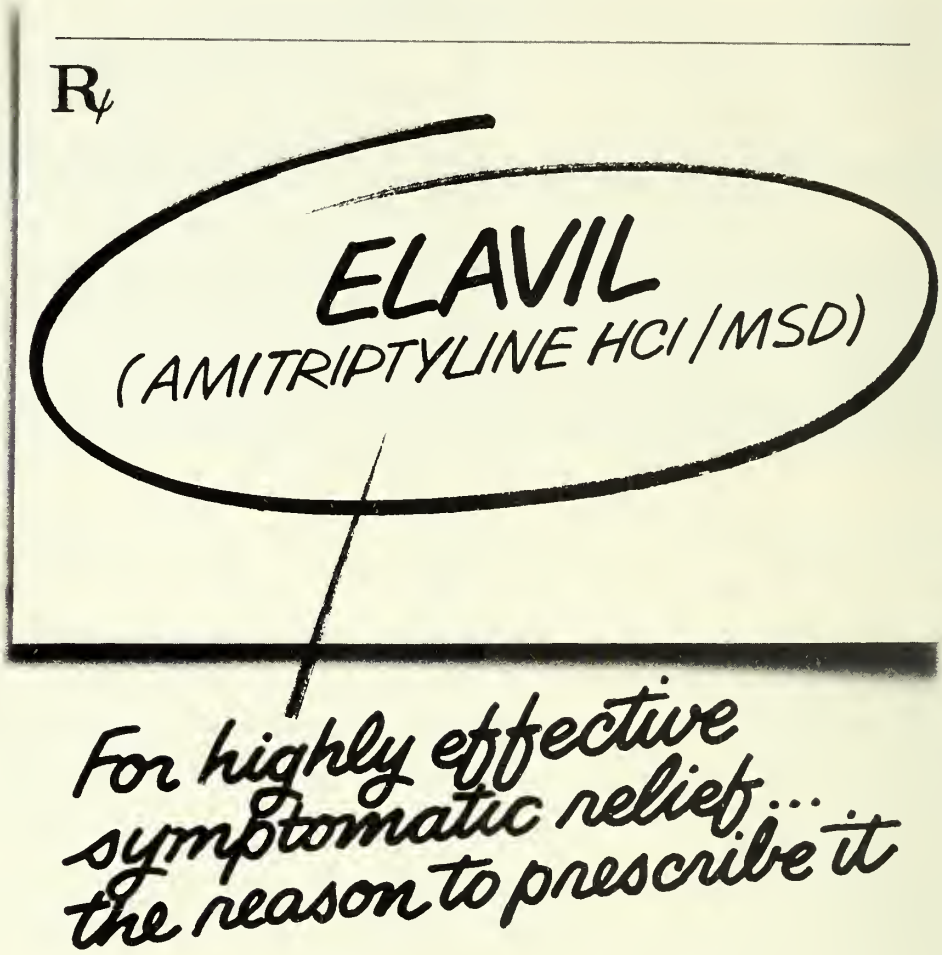
BEHAVIOROYNE

In the treatment of clinically significant depression



For highly effective symptomatic relief... the reason to prescribe it

Now added dosage versatility...

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ELAVIL
(AMITRIPTYLINE HCl/MSD)

h.s.

An important alternative in fitting the medication to the patient's needs

Once-a-day dosage at bedtime is an appropriate way to start—and maintain—many patients on therapy. Of course, ELAVIL may be administered two, three, or four times as well as once a day. This dosage versatility allows prescribing precisely for the patient's needs.

Once-a-day dosage schedule for adult outpatients

Therapy should be initiated with 50 mg to 100 mg at bedtime. This may be increased by 25 or 50 mg added to the bedtime dose as necessary to a maximum daily dose of 150 mg. The usual maintenance dose is 50 to 100 mg a day given at bedtime, though in some patients, 40 mg per day is sufficient.

- **Greater patient compliance**

The simplicity of once-a-day dosage at bedtime makes it easier for patients to adhere to a regimen—an especially important consideration in depressed patients whose self-motivation may be at a low ebb.

Should not be used during the acute recovery phase following myocardial infarction; in patients hypersensitive to it; in those who have received an MAOI within two weeks; or in children under 12. Patients with cardiovascular disorders should be watched closely. Safe use during pregnancy and lactation has not been established. The drug may impair mental or physical abilities required in the performance of hazardous tasks and may enhance the response to alcohol. Since suicide is a possibility in any depressive illness, patients should not have access to large quantities of the drug. Hospitalize as soon as possible any patient suspected of having taken an overdose.

once a day at bedtime

Please see addendum on following page for other details of dosage and administration including divided daily doses, dosage in hospitalized patients, and dosage in elderly and adolescent patients.

TABLETS: 10 mg, 25 mg, and 50 mg INJECTION: 10 mg per ml

ELAVIL®

(AMITRIPTYLINE HCl | MSD)

MSD
MERCK SHARP & DOHME

For a brief summary of prescribing information, please see following page.

ELAVIL®
(AMITRIPTYLINE HCl | MSD)

added dosage versatility in clinically significant depression

Contraindications: Known hypersensitivity. Should not be given concomitantly with a monoamine oxidase inhibitor or within at least 14 days following the discontinuance of a monoamine oxidase inhibitor since hyperpyretic crises, severe convulsions, and deaths have occurred. When used to replace a monoamine oxidase inhibitor, initiate dosage of amitriptyline HCl cautiously with gradual increase in dosage until optimum response is achieved. Not recommended during the acute recovery phase following myocardial infarction.

Warnings: May block the antihypertensive action of guanethidine or similarly acting compounds. Should be used with caution in patients with a history of seizures or urinary retention, or with angle-closure glaucoma or increased intraocular pressure; in patients with angle-closure glaucoma, even average doses may precipitate an attack. Patients with cardiovascular disorders should be watched closely; arrhythmias, sinus tachycardia, and prolongation of the conduction time have been reported, particularly with high doses; myocardial infarction and stroke have been reported with drugs of this class. Close supervision is required for hyperthyroid patients or those receiving thyroid medication. May impair mental and/or physical abilities required for performance of hazardous tasks, such as operating machinery or driving a motor vehicle. Safe use during pregnancy and lactation has not been established; in pregnant patients, nursing mothers, or women who may become pregnant, weigh possible benefits against possible hazards to mother and child. Not recommended for patients under 12 years of age.

Precautions: Schizophrenic patients may develop increased symptoms of psychosis; patients with paranoid symptomatology may have an exaggeration of such symptoms; manic depressive patients may experience a shift to the manic phase. In these circumstances, the dose of amitriptyline HCl may be reduced or a major tranquilizer, such as perphenazine, may be administered concurrently.

When given with anticholinergic agents or sympathomimetic drugs, including epinephrine combined with local anesthetics, close supervision and careful adjustment of dosages are required. Use cautiously in patients receiving large doses of ethchlorvynol, since transient delirium has been reported on concurrent administration. May enhance the response to alcohol and the effects of barbiturates and other CNS depressants. The possibility of suicide in depressed patients remains during treatment and until significant remission occurs; this type of patient should not have easy access to large quantities of the drug. Concurrent electroshock therapy may increase the hazards associated with such therapy; such treatment should be limited to patients for whom it is essential. When possible, discontinue the drug several days before elective surgery. Both elevation and lowering of blood sugar levels have been reported.

Adverse Reactions: *Note:* Included in this listing are a few adverse reactions not reported with this specific drug. However, pharmacological similarities among the tricyclic antidepressant drugs require that each reaction be considered when amitriptyline is administered. *Cardiovascular:* Hypotension, hypertension, tachycardia, palpitation, myocardial infarction, arrhythmias, heart block, stroke. *CNS and Neuromuscular:* Confusional states; disturbed concentration; disorientation; delusions; hallucinations; excitement; anxiety; restlessness; insomnia; nightmares; numbness, tingling, and paresthesias of the extremities; peripheral neuropathy; incoordination; ataxia; tremors; seizures; alteration in EEG patterns; extrapyramidal symptoms; tinnitus. *Anticholinergic:* Dry mouth, blurred vision, disturbance of accommodation, constipation, paralytic ileus, urinary retention, dilatation of urinary tract. *Allergic:* Skin rash, urticaria, photosensitization, edema of face and tongue. *Hematologic:* Bone marrow depression including agranulocytosis, leukopenia, eosinophilia, purpura, thrombocytopenia. *Gastrointestinal:* Nausea, epigastric distress, vomiting, anorexia, stomatitis, peculiar taste, diarrhea, parotid swelling, black tongue. *Endocrine:* Testicular swelling and gynecomastia in the male, breast enlargement and galactorrhea in the female, increased or decreased libido, elevation and lowering of blood sugar levels. *Other:* Dizziness, weakness, fatigue, headache, weight gain or loss, increased perspiration, urinary frequency, mydriasis, drowsiness, jaundice, alopecia. *Withdrawal Symptoms:* Abrupt cessation of treatment after prolonged administration may produce nausea, headache, and malaise; these are not indicative of addiction.

Overdosage: Hospitalize as soon as possible all patients suspected of having taken an overdose. Treatment is symptomatic and supportive. In addition, the intravenous administration of 1 to 3 mg physostigmine salicylate has been reported to reverse the symptoms of tricyclic antidepressant poisoning.

How Supplied: Tablets containing 10 mg and 25 mg amitriptyline HCl, in single-unit packages of 100 and bottles of 100, 1000, and 5000; tablets containing 50 mg amitriptyline HCl, in single-unit packages of 100 and bottles of 100 and 1000; for intramuscular use, in 10-ml vials containing per ml: 10 mg amitriptyline HCl, 44 mg dextrose, 1.5 mg methylparaben and 0.2 mg propylparaben as preservatives, and water for injection q.s. 1 ml.

For more detailed information, consult your MSD representative or see full prescribing information. Merck Sharp & Dohme, Division of Merck & Co., INC., West Point, Pa. 19486

addendum

MSD MERCK SHARP & DOHME

ELAVIL®
(AMITRIPTYLINE HCl | MSD)

dosage forms for differing patient needs

25 mg (yellow)

This tablet may prove useful for initial therapy in adult outpatients. Starting dosage is usually 75 mg daily in divided doses or 50 to 100 mg once a day at bedtime. If necessary, this dosage may be increased gradually to a total of 150 mg a day. When doses are divided, dosage increases are made preferably in the late afternoon or at bedtime. A sedative effect may be apparent before the antidepressant effect is noted. An adequate therapeutic effect may take as long as 30 days to develop.

50 mg (beige)

The 50-mg tablet may be advantageous whenever higher dosages are required, or when the single daily dose is given at bedtime. The 50-mg tablet may also be convenient for many hospitalized patients who may need 100 mg a day initially. In these patients, dosage may be increased gradually to 200 mg a day if necessary. A small number of hospitalized patients may need as much as 300 mg a day.

10 mg (blue)

Because lower doses are generally recommended for adolescents and elderly patients, the 10-mg tablets may be most serviceable. Ten mg three times a day with 20 mg at bedtime may be satisfactory in adolescent and elderly patients who do not tolerate higher doses.

INJECTION
10 mg per ml

For patients unable or unwilling to take tablets, the injectable form may be suitable initially. The tablets should replace the injection as soon as possible. Initial intramuscular dosage is 20 to 30 mg (2 to 3 ml) four times a day. When Injection ELAVIL is administered intramuscularly, the effects may appear more rapidly than with oral administration.

Usage in Children: In view of the lack of experience in children, this drug is not recommended at the present time for patients under 12 years of age.

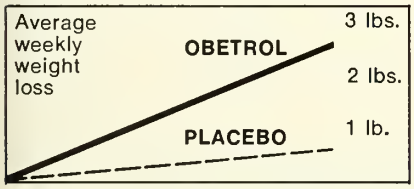
EFFECTIVE APPETITE DEPRESSANT with predictable pharmacological action

OBETROL® II

Single entity amphetamine product. Each OBETROL-10 (10 mg. tablet) contains: dextroamphetamine saccharate 2.5 mg., amphetamine aspartate 2.5 mg., dextroamphetamine sulfate 2.5 mg., amphetamine sulfate 2.5 mg. OBETROL-20 (20 mg. tablets) contain twice this potency.

Average weight loss of 2.15 lbs per week compared in clinical studies against a placebo.

CONTROLLED STUDY —
72 CASES 4 WEEKS' RESULTS



Obetrol eases the discomfort of adherence to a restricted diet in individuals who are well motivated to reduce their food intake.

Clinical studies disclose amphetamines to be the most dependable drug in a weight-reduction regimen compared to other anorexigenic agents.

Amphetamines have a significant potential for abuse. In view of their limited short-term anorectic effect and rapid development of tolerance, they should be used with extreme caution and only for limited periods of time in weight reduction programs.

Actions: Amphetamines are sympathomimetic amines with CNS stimulant activity. Peripheral actions include elevation of systolic and diastolic blood pressures and weak bronchodilator and respiratory stimulant action. The anorectic effect diminishes after a few weeks.

Indications: Exogenous obesity, as a short term (a few weeks) adjunct in a regimen of weight reduction based on caloric restriction. For patients in whom obesity is refractory to other measures.

Contraindications: Advanced arteriosclerosis, symptomatic cardiovascular disease, moderate to severe hypertension, hyperthyroidism, known hypersensitivity or idiosyncracy to the sympathomimetic amines. • Agitated states. • Patients with a history of drug abuse. • During or within 14 days following the administration of monoamine oxidase inhibitors, hypertensive crises may result.

Warnings: Tolerance to the anorectic effect usually develops within a few weeks. When this occurs, the recommended dose should not be exceeded in an attempt to increase the effect, rather, the drug should be discontinued. Amphetamines may impair the ability of the patient to engage in potentially hazardous activities such as operating machinery or driving a motor vehicle; the patient should therefore be cautioned accordingly.

Precautions: Caution is to be exercised in prescribing amphetamines for patients with even mild hypertension. Insulin requirements in diabetes mellitus may be altered in association with the use of amphetamines and the concomitant dietary regimen. Amphetamines may decrease the hypotensive effect of guanethidine. The least amount feasible should be prescribed or dispensed at one time in order to minimize the possibility of overdosage.

Adverse Reactions: *Cardiovascular:* Palpitation, tachycardia, elevation of blood pressure. Central nervous system: Overstimulation, restlessness, dizziness, insomnia, euphoria, dysphoria, tremor, headache; rarely, psychotic episodes at recommended doses. *Gastrointestinal:* Dryness of the mouth, unpleasant taste, diarrhea, other gastrointestinal disturbances. Anorexia and weight loss may occur as undesirable effects when amphetamines are used for other than the anorectic effect. *Allergic:* Urticaria. *Endocrine:* Impotence, changes in libido.

Dosage and Administration: Regardless of indication, amphetamines should be administered at the lowest effective dosage and dosage should be individually adjusted. Late evening medication should be avoided because of the resulting insomnia.

1. Narcolepsy: Usual dose 5 to 60 milligrams per day in divided doses.
2. Minimal brain dysfunction:
   a. Not recommended for children under 3 years of age.
   b. Children from 3 to 5 years of age: 2.5 milligrams daily, raised in increments of 2.5 milligrams at weekly intervals until optimal response is obtained.
   c. Children 6 years of age and older, 5 milligrams, once or twice daily, increased in increments of 5 milligrams at weekly intervals. Only in rare cases will it be necessary to exceed a total of 40 milligrams per day.
3. Obesity: Usual adult dose 5 to 30 milligrams per day in divided doses.

Overdosage: Manifestations of acute overdosage with amphetamines include restlessness, confusion, assaultiveness, hallucinations, panic states. Fatigue and depression usually follow the central stimulation. Cardiovascular effects include arrhythmias, hypertension or hypotension, and circulatory collapse. Gastrointestinal symptoms include nausea, vomiting, diarrhea, and abdominal cramps. Fatal poisoning usually terminates in convulsions and coma.

Management of acute amphetamine intoxication is largely symptomatic and includes lavage and sedation with a barbiturate. Experience with hemodialysis or peritoneal dialysis is inadequate to permit recommendations in this regard.

Availability: Supplied in bottles of 100; 500 and 1,000 tablets.

CAUTION: FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION.

January 1973

Comprehensive informational brochure available upon written request. Prescribe Obetrol for appetite control.

OBETROL Pharmaceuticals Division/Rexar Pharmacal Corp. Valley Stream, New York 11582

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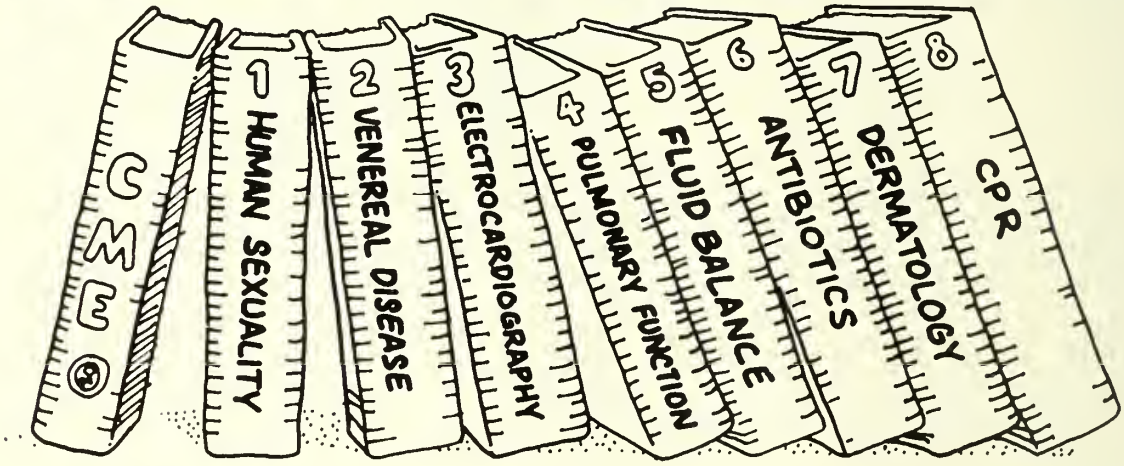

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8. Basic and Advanced Life Support — Cardiopulmonary Resuscitation (CPR)

*Courses 1 through 7 are 6 hours each; each is presented twice (once on Saturday, once on Sunday). Course No. 8 is a 12-hour course that runs both days.

Sites

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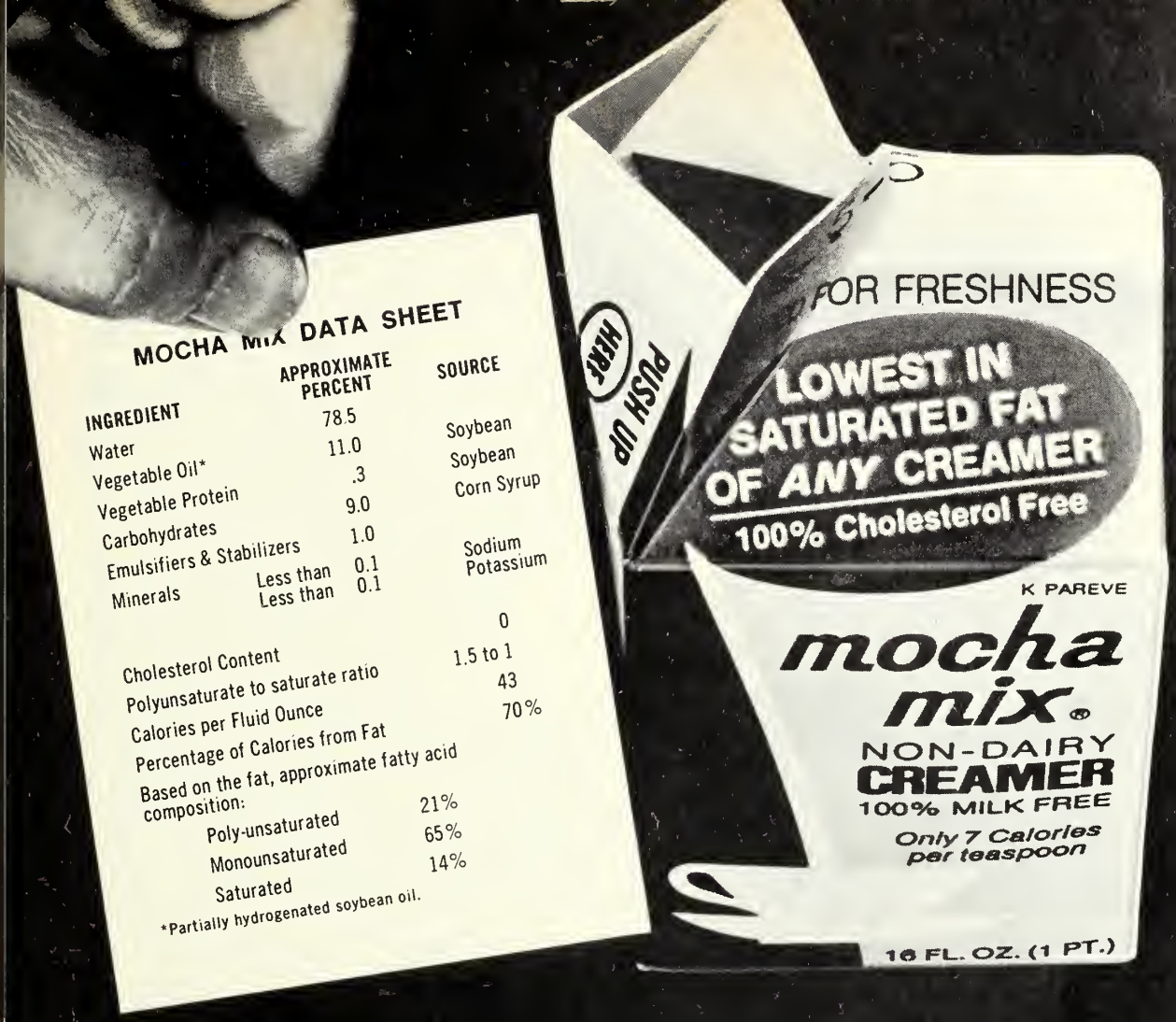

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Ampoules, equivalent to 1 Gm. of cefazolin

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Additional information available to the profession on request.

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THE WESTERN
Journal of Medicine

Refer to: de Groot WPH: Diagnosis of carcinoma and benign cysts of the breast—The value of needle aspiration. West J Med 122:99-103, Feb 1975

Diagnosis of Carcinoma and Benign Cysts of the Breast

The Value of Needle Aspiration

WALTER P. H. de GROOT, MD, *Seattle*

Diagnosis of solid breast masses by needle aspiration with cytological examination of the aspirate has been practiced for some time in several centers in this country and abroad. It has been proposed as an alternative to the conventional excisional biopsy for the diagnosis of carcinoma of the breast.

At the same time, simple needle aspiration of benign cysts as an office procedure has gained new favor as a means of proving the presence of benign disease at the first office visit and thus avoiding the loss of time, and the expense and worry of surgical excision in a hospital. From a review of the reliability and practical usefulness of both methods, it is concluded that aspiration biopsy for the diagnosis of carcinoma is less reliable than conventional excisional biopsy and offers very little practical advantage.

Simple aspiration of cysts, on the other hand, appears to offer a true saving of time, expense and worry, and to be a reliable method, if used properly.

ASPIRATION OF BREAST MASSES has been practiced by surgeons for many years, but its application until recently was limited, as the only lesions aspirated were cysts or lesions presumed to be cysts.

If aspiration of what clinically appeared to be a cyst yielded clear fluid and the mass then disappeared, a benign cyst was considered proven and no further diagnostic procedures, notably excisional biopsy, were deemed necessary.

Moreover, therapy was automatically included, as a successful aspiration caused the worrisome mass to disappear.

The method of the procedure was simple, its evaluation was subjective and for all practical purposes it could not be reviewed and evaluated by others, while there was a total absence of any tangible substrate.

Until recently, aspiration biopsy was for the most part a procedure used in their offices by some physicians and totally ignored by others. Of late, however, pathologists have become increasingly interested in the needle aspiration of practically all types of breast lesions, including, and even with preference, solid masses. Hence the aspirates are now being examined by the latest refined, cytologic techniques.*

Submitted May 2, 1974.

Reprint requests to: W. P. H. de Groot, MD, 1019 Madison Street, Suite 543, Seattle, WA 98104.

*Needle *aspiration* biopsy should not be confused with the well-established needle *core* biopsy, in which a small incisional biopsy specimen is removed with a cylindrical knife. The specimen is morphologically intact and is studied histologically on permanent or frozen section. In aspiration biopsy the specimen is a minute amorphorus aspirate, without architecture, allowing only cytological examination.

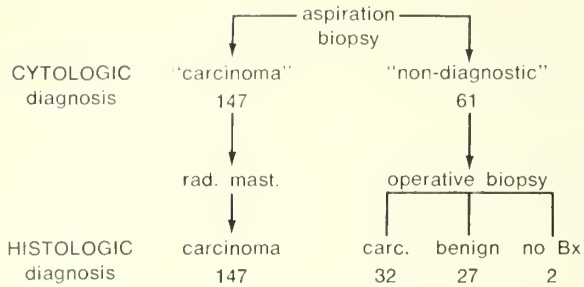

Chart 1.—Results of aspiration biopsy—208 cases (from Rosen et al,[1] 1972).

At first this was done out of an interest in comparing the histologic diagnosis based on conventional excisional biopsy with the cytologic diagnosis of the aspirates and trying to estimate the relative accuracy.

At first the possibility of using cytologic rather than histologic examination was suggested for cases in which conventional biopsy was impossible or less desirable or was unnecessary—cases in which the patient forbade operation or radiotherapy was to be given for obvious advanced carcinoma. As the technique became refined, however, and the confidence of the investigators increased, some of them proceeded to make the diagnosis of carcinoma and advise a radical surgical procedure solely on the basis of cytologic examination of aspirate.[1-5] Those who advocate this method stress the advantages of minimal invasiveness, the saving of time, and the complete avoidance of surgical procedure and admission to hospital if the lesion is found to be benign.[3,5,6] At the Radiumhemmet in Stockholm, all palpable breast lesions are aspirated for biopsy; if the cytologic diagnosis of carcinoma seems sufficiently certain, it serves as an indication for radical operation.[2,4]

In this country, Rosen reported a series of 147 radical mastectomies done on the basis of cytologic diagnosis only.[1]

At the same time, the original simple aspiration of cysts, done as an office procedure to rule out malignant disease, has gained renewed favor among surgeons.[7-12] While it was always gratifying to be able to relieve the patient's worry in a few minutes, and avoid a surgical procedure in hospital, nowadays the economical factors involved are becoming increasingly important. Some observers, however, consider the method too primitive, subjective and unreliable for excluding malignant disease, and it has become rather controversial. The modern surgeon, then, is offered two uses of needle aspiration biopsy of the breast —one a new refined technique, requiring great expertise of the pathologist, for use in lieu of excisional biopsy to prove malignant disease; the other an old, simple method of ruling out cancer at the first office visit.

How reliable are these methods and what are the true practical advantages of either one?

Aspiration to Prove the Presence of Carcinoma

Rosen et al[1] reported a series of 208 aspirations of masses clinically diagnosed as carcinoma. Whenever the cytologic diagnosis of the aspirates was carcinoma, these investigators confidently proceeded with radical mastectomy. All mastectomy specimens were subjected to histological examination so that the cytologic diagnosis could be verified. Whenever the aspirate was not unequivocally malignant, it was considered non-diagnostic, and the mass was subjected to conventional excisional biopsy with histologic examination. The results are schematically represented in Chart 1.

When a cytological diagnosis is accepted in deciding whether carcinoma is present and radical mastectomy should be done, it is obvious that either a false positive or a false negative diagnosis of carcinoma constitutes a true danger, one because it can lead to unnecessary mastectomy, the other because treatment would not be given though needed.

Rosen solved the problem of the false negatives simply by not accepting a "negative" diagnosis. The absence of obvious malignancy was not interpreted as evidence a lesion was benign, but only as "non-diagnostic." In all such instances conventional biopsy was done and several malignant lesions missed by previous cytological examination were diagnosed.

This appears to be the only safe way to deal with a "benign" or a "negative" diagnosis, for the incidence of false negatives generally is rather high, much higher than that of false positives. This is to be expected, because it is not only easier to be sure cytologically that malignant change is present than that it is not, but also because false negatives often probably are simply due to missing the site of malignant disease with the aspirating needle.

Franzen and Zajicek at the Radiumhemmet in Oslo had an incidence of 10.8 percent false negatives in 873 cases of proven carcinoma[2] and found in a review of the literature that the average incidence of false negatives is 12.8 percent. Thus, if

aspirated specimens and cytological examination are relied upon, somewhere around 12 percent of carcinomas can escape detection, at least at the first presentation of the mass.

Even more significant are the false positives, because they lead to radical mastectomy though the lesion is benign. In Rosen's series, not one false positive diagnosis of carcinoma was made, which was probably again owing to the use of conventional biopsy in any case in which the aspirate was not clearly malignant.

In other series, however, false positives did occur.[2,3,6] Franzen and Zajicek,[2] whose own incidence of false positives was only 0.1 percent, found in their review that the average was 0.9 percent, but ranged as high as 4.1 percent in some series.[2] This would mean that if aspiration biopsy is the only diagnostic procedure, as many as four of every hundred women examined may be subjected to unnecessary radical mastectomy.

Should Aspiration Biopsy Replace Excisional Biopsy?

When evaluating the usefulness of a new diagnostic procedure, one should consider the advantages it offers to patient and surgeon over the methods already in use, as well as its relative reliability. A considerable factor is the degree of expertise the method requires and the incidence of error in the hands of physicians who are as expert as can reasonably be expected.

It appears, then, that two conditions have to be met for the method to be acceptably reliable: (a) that only clinically malignant masses be aspirated to confirm malignant change, and (b) that all masses which are not unequivocally malignant be excised and histologically examined. As was previously noted, Rosen[1] applied these two rules and for that reason had no false positives—though of course this injunction severely limits the usefulness of the procedure as it is apparent that all patients undergo a surgical procedure in either case.

That a high degree of expertise is required is generally admitted.[1-3,6] Hence, reliability depends far more on special knowledge than does making a histologic diagnosis.

In summary, then, although a fascinating and challenging method, the cytological diagnosis of carcinoma at best seems to offer no advantages over the present histological method, while there is a greater chance of needless mastectomy on the one hand and of missing carcinoma on the other.

Even in the case of a patient's refusing operation, or if confirmation of an obvious advanced carcinoma is desired, a standard core needle biopsy would seem preferable. The latter gives an adequate fragment of tissue for histological examination, while a patient who refuses operation but will accept aspiration is not likely to consider a core needle biopsy any more invasive.

A panel discussing the team approach to the evaluation of breast masses, during the recent 13th Annual Conference on Early Detection and Treatment of Breast Cancer, came to the same conclusions.[13]

Aspirations of Benign Cysts

The aspiration of cysts differs from the aspiration of solid masses first of all in that its purpose is not to see whether malignant change is present, but to confirm the clinical impression that malignancy is absent. Second, whereas in aspiration of solid masses the cytological examination is obviously the decisive part of the procedure, the fluid aspirated from cysts is not examined microscopically at all if it is clear, but is simply discarded. The rationale is that clear fluid is sufficient proof of benignity.

Although aspiration of cysts has been advocated by many investigators,[7-12] several objections have been raised against using it in lieu of surgical excision, the main arguments being: (1) that women with fibrocystic disease have an increased incidence of carcinoma, (2) that a cyst may hide an underlying carcinoma, (3) that there may be a carcinoma in the wall of the cyst.

While many observers have claimed an increased incidence of carcinoma in fibrocystic disease,[10,14-16] others[17-19] have denied this relationship. An interesting study is that of Devitt,[19] who concluded that a relationship does not exist and that there is "no need to terrorize patients with fibrocystic disease by advising continual follow-up examination."

Even more important possibly is the realization that in the present discussion it is, logically speaking, of no importance whether the patient is *prone* to carcinoma *somewhere* in either breast; what decides is whether she has a carcinoma *now* and *at the exact site* of the cyst that has brought her to examination. This shifts the problem back to the other two questions, namely, how likely is the presence of a carcinoma in the wall of the cyst, and could the cyst hide a carcinoma?

Rose[20] reported two cases of carcinoma in the actual wall of a cyst, but judging from the litera-

ture such cases are rare. As to the question of a cyst's hiding a nearby carcinoma, Rose (in the same paper) reported three cases in which this occurred. Although aspiration was not carried out, Rose said that even if it had been, the carcinoma would not have been palpable because of adjacent smaller cysts.

In that light it seems reasonable to point out that if surgical biopsy were done the resultant scarring would even more interfere with subsequent digital examination of the surrounding area, which should be of special concern to precisely those who believe that fibrocystic disease predisposes to carcinoma. It is our belief that, on the contrary, in most cases the aspiration of a cyst will permit more adequate palpation of the area involved. Moreover, if a carcinoma is so small that it escapes detection by the examining finger even when attention is directed to the specific area, a question that comes up is how one could have detected so small a lesion elsewhere in the same or the other breast, or at another time.

This simply emphasizes the necessity of having to decide, whenever one is examining breasts, what constitutes a mass and what does not, or, where does normal "lumpiness" end and a discrete mass start? For those who feel they cannot make that decision, the only logical way out would be either to do an endless number of tissue examinations (with ever-increasing scarring and resultant suspiciousness of the remaining tissue) or carry out bilateral mastectomy, which may be proper in extreme cases but seems a rather drastic procedure to use in all cases of fibrocystic disease.

Of special interest in this respect is that Haagensen,[10] although of the opinion that the incidence of carcinoma in fibrocystic disease is four times as great as in normal breasts, nonetheless advocates aspiration of cysts, as long as they clinically appear to be only that.

One might also abandon all theoretical considerations and simply ask the practical question: In how many breasts does carcinoma develop after cyst aspiration? Patey,[7] following 65 patients with cyst aspiration, found the development of only one carcinoma, and that in the opposite breast. Vanden Berg[9] and Hermann[21] reported similar findings.

Practical Questions About Cyst Aspiration

A few practical questions related to the aspiration of cysts are:

1. When does an aspirate not qualify as benign and should a conventional biopsy follow?

2. How often can aspiration of the same cyst be repeated?

3. Should the aspirate be cytologically examined?

4. Should the first mass always be excised?

And to answer those questions:

1. There is general agreement that aspiration should be followed by excisional biopsy when (a) no fluid is aspirated ("dry tap"), (b) blood is aspirated, (c) the mass does not completely disappear.[8,10,11]

2. Most observers believe that the cyst should be excised after two[11] or three[8] aspirations. Others are of the opinion the procedure can be repeated endlessly.[12] This may be more of a theoretical than a practical problem, as exactly the same cyst will rarely refill twice, according to Haagensen, who said: "I have no satisfactory explanation as to why this does not happen, but it is a fact that it does not."[10]

Moreover, if the same cyst refills twice, probably neither the patient nor the physician will be psychologically able to forego surgical excision any longer, and it could certainly not be said that nonoperative treatment had not been tried.

3. Although in most large series cytological examination of the aspirated fluid has been abandoned,[11,12] the surgeon who does aspiration only occasionally might find it of added psychological benefit for the patient, and possibly also for himself, to have a cell block made of the aspirate. The modern sophisticated patient is used to having everything that is removed from her body sent to a pathologist, and the information that no malignant change was found microscopically gives her an added sense of security, at little additional cost.

4. It is often stated that the first appearing mass in any given patient should be excised "to establish the diagnosis of fibrocystic disease."

We cannot help thinking that this dictum is more the product of the psychological than the rational part of surgical decision-making, and that the surgeon, having been brought up with the necessity of surgical excision and somewhat fearful to give it up completely, throws in at least one excision.

Logically speaking, each succeeding cyst is an entity of its own, with its own possibility of carcinoma, and if one relies on a satisfactory aspiration

at the second and third occurrence, why not the first time?

Conversely, if an excision is required to prove the existence of fibrocystic disease in a given breast, each succeeding mass would again require an excision to prove that the fibrocystic process is still the only pathologic process present. The presence of fibrocystic disease per se can really adequately be determined by palpation and, if necessary, mammography; and whether a carcinoma is present in addition constitutes a problem the second time just as much as the first. The question really is whether one does or does not trust a properly executed aspiration to answer that question.

Is Aspiration of Cysts Safe and Useful?

Aspiration should not be used to see whether any given breast mass might be a cyst, but merely to confirm the clinical impression that it is one.

If blood or no fluid at all is aspirated, or if the mass does not completely disappear, a standard excisional biopsy should be performed.

The expertise required is the ability of the surgeon to determine whether the mass has indeed disappeared. This is a competence which any surgeon should possess, for he has to answer the question "Mass or not?" every time he examines a female breast, whether or not he practices aspiration.

If used this way, aspiration of cysts is a simple and reliable way to quickly end the worry over a mass, without the expense, the loss of time and the risk entailed in surgical procedures in a hospital.

Conclusions

Aspiration biopsy of solid breast masses with cytological examination of the aspirate for the routine diagnosis of carcinoma does not appear to have any practical advantages over conventional excisional biopsy with histological examination. Even in the case of a patient's refusing surgical excision of a tissue specimen, standard core needle biopsy might be acceptable and would seem more reliable than aspiration biopsy.

Aspiration to confirm the presence of cysts, if used judiciously, is a safe and simple office procedure which can quickly end worry and prevent the expense, risk and time loss of needless operation in a hospital.

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Evaluation Before Thoracotomy

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When a thoracotomy is being considered, the physician must first determine whether the lesion is potentially resectable. However, an equally important decision is whether the patient can tolerate pulmonary resection if there are other serious underlying medical problems. In any patient with signs or symptoms of pulmonary disease, a spirogram, arterial blood gas study and electrocardiogram should be done as part of the routine preoperative evaluation. The detection of abnormal pulmonary function should prompt preoperative institution of respiratory care to optimize maximally a patient's cardiorespiratory status before operation. If any of several indicators of a high risk of postoperative cardiopulmonary problems are found, split pulmonary function studies should be done to determine whether the lung remaining after resection will have adequate ventilation and perfusion. Xenon radiospirometry is preferable to bronchospirometry and right heart catheterization because of its noninvasiveness. Resection should not be undertaken in the presence of a predicted postoperative forced expiratory volume in one second (FEV_1) less than 0.8 liter, an arterial carbon dioxide partial pressure ($PaCO_2$) greater than 45 mm of mercury or Xenon scans which show poor ventilation/perfusion ($\dot{V}/\dot{Q}$) matchup in what would be the remaining lung after resection. A case is reported which shows the value of this approach to preoperative evaluation in determining the risk of postoperative problems.

WHEN A THORACOTOMY is contemplated in a patient with pulmonary disease two questions need to be considered. First, is the pulmonary lesion resectable? For instance, if the patient has a bronchogenic carcinoma can the lesion be completely removed or is there evidence for nonresectability (for example, vocal cord paralysis resulting from tumor invasion of the mediastinum, diaphragmatic paralysis from phrenic nerve involvement or pleural effusion secondary to tumor involvement of the pleura).

If the answer to the first question is yes, then one must ask a second question. Is the patient an acceptable surgical risk? Does the patient have borderline respiratory insufficiency, severe ischemic heart disease, left ventricular failure or other medical problems which would lead to a high incidence of postoperative morbidity and mortality? It gives little comfort to a physician to be

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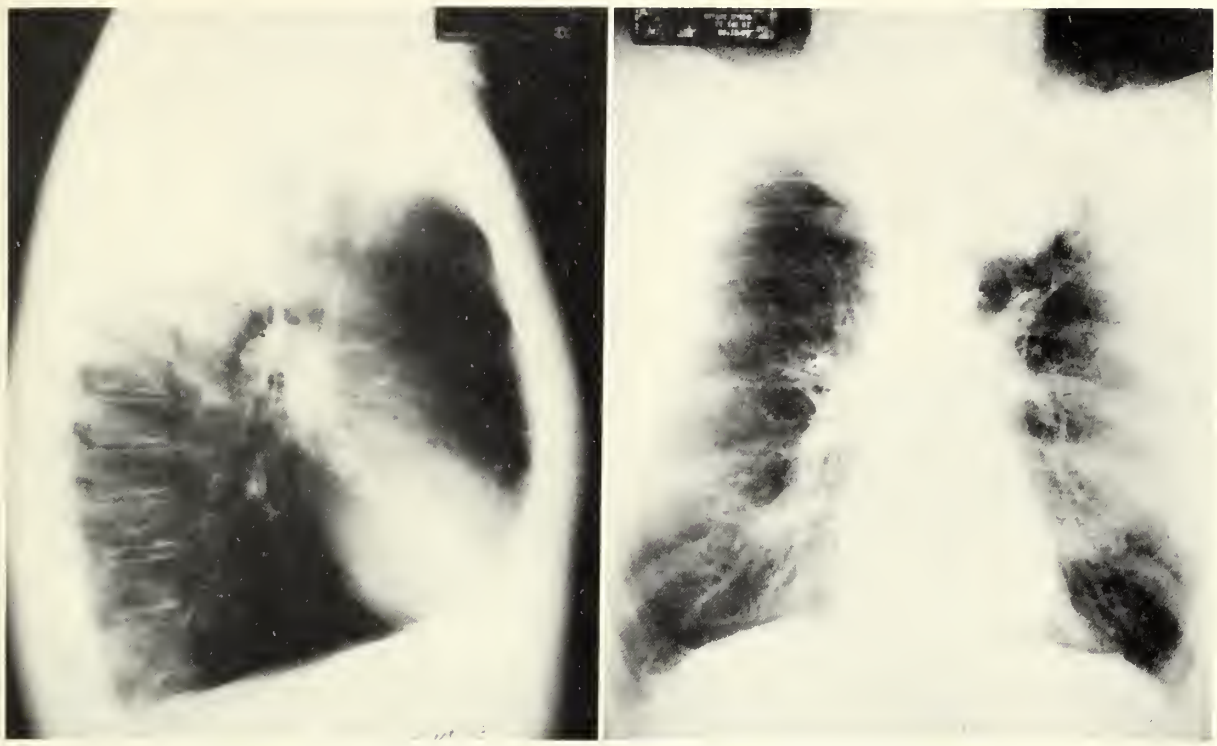

Figure 1.—Preoperative posteroanterior and lateral x-ray films of chest.

able to resect a pulmonary lesion but then end up with a patient who is a cardiorespiratory cripple.

In a patient with no preoperative evidence of cardiac or pulmonary disease, the risk of thoracotomy is minimal. However, in a patient with significant chronic obstructive lung disease, one must very carefully evaluate the patient to determine if he is an acceptable surgical candidate. It is not with the question of resectability that most physicians have difficulty. Rather it is with the question of acceptability as a surgical risk where a vast amount of confusion exists. An objective approach to preoperative evaluation is outlined, and a case history presented which exemplifies the prethoracotomy workup.

Report of a Case

The patient is a 58-year-old married Caucasian man who presented with a left upper lobe mass on x-ray examination of the chest. The patient was told twelve years before admission to hospital that he had emphysema, and has been on a complete program including intermittent positive-pressure breathing (IPPB) treatments at home for the past five years. The patient complained of a shortness of breath on climbing one flight of stairs or walking one block at a normal pace. Because of hemoptysis, a chest x-ray film was taken which showed a left upper lobe mass, and the patient was referred to Loma Linda University Medical Center for further evaluation.

On examination at the time of admission, the patient was found to be alert, cooperative, well developed and well nourished, with no evidence of acute distress. It was noted that the accessory inspiratory muscles were being used on quiet breathing. On examination of the chest, a notably increased anteroposterior diameter was found, with decreased breath sounds bilaterally. There were bilateral expiratory wheezes with a prolonged expiratory time on quiet breathing. Cardiac examination showed a regular sinus rhythm with no murmurs or ventricular heaves. There was no evidence of either left or right ventricular decompensation on the physical examination.

An x-ray film of the chest showed moderate pulmonary hyperexpansion and a left upper lobe mass (Figure 1). The admitting spirogram showed severe obstructive pulmonary disease with improvement following bronchodilator aerosol (Table 1). The admitting arterial blood gas study on room air showed a normal arterial oxygen partial pressure (PaO_2) for the patient's age, and normal acid-base data (Table 2). An electrocardiogram showed nonspecific ST-T wave changes. Bronchoscopy and mediastinoscopy were

TABLE 1.—*Spirographic Data Preoperatively and Two Months Postoperatively*

		PREOPERATIVE				POSTOPERATIVE			
		Pre Bronchodilator		Post Bronchodilator		Pre Bronchodilator		Post Bronchodilator	
	Pred	Obs	Percent Pred	Obs	Percent Pred	Obs	Percent Pred	Obs	Percent Pred
FVC (L)	4.08	3.40	84	4.04	99	2.47	61	3.14	78
FEV_1 (L)	3.06	.83	27	1.07	35	.95	31	1.01	33
$FEV_1 \times 100$/OBS VC	≥75%	24%	..	26%	..	39%	..	32%	..
MVV (L/MIN)	107	35	33	45	42	37	36	52	50
MMF (L/SEC)	3.3	.2	7	.3	10	.3	10	.4	13

FVC (Forced vital capacity)
FEV_1 (Forced expiratory volume in one second)
$FEV_1 \times 100$/OBS VC (Forced expiratory volume in one second times 100 divided by the observed forced vital capacity)
MVV (Maximal voluntary ventilation)
MMF (Maximal midexpiratory flow rate)

TABLE 2.—*Arterial Blood Gas Data Preoperatively and Two Months Postoperatively*

	Normals	Pre-operative Values	Post-operative Values
Plasma pH	7.35 - 7.45	7.44	7.39
Plasma PO_2	74-82 mm Hg	74	77
Plasma PCO_2	35-45 mm Hg	37	42
O_2 Saturation	≥94%	93.5	94
O_2 Content	16-20 Vol. %	15.6	17.2
Plasma HCO_3	22-26 mEq/l	25	25
Base-Excess	−2 to +2 mEq/l	1	0

done and results of these were negative. No physical or laboratory findings were present to indicate that this lesion was nonresectable.

The major question to be answered was whether or not the patient was an acceptable surgical candidate. Would the patient be left a cardiorespiratory cripple following thoracotomy if in fact he could survive pulmonary resection? A Xenon ventilation/perfusion ($\dot{V}/\dot{Q}$) study was done. The ventilation study showed decreased ventilation in both apices with the equilibrium phase showing relatively uniform ventilation throughout both lungs, except for the left apex which never ventilated well. The perfusion scan showed pronounced perfusion deficits in the upper lung fields bilaterally with nonuniformity of both lower lung fields. As noted, in spite of the severe obstructive airway problem seen on the spirogram, the patient's arterial blood gas study showed normal PaO_2 and arterial carbon dioxide partial pressure ($PaCO_2$) values. This was objective evidence that in spite of a severe obstructive airway defect, the patient had adequate $\dot{V}/\dot{Q}$ matchup throughout the lung fields.

Since the Xenon $\dot{V}/\dot{Q}$ scan showed that there was little function in the left upper lobe area, it was felt that the majority of the patient's $\dot{V}/\dot{Q}$ matchup would be preserved in spite of a left upper lobectomy. Therefore, a decision to proceed with the surgical procedure was made. However, for the week before thoracotomy respiratory care was instituted (including an oral bronchodilator, IPPB with aerosolized bronchodilator, an expectorant and, in light of the wheezing found on physical examination and bronchodilator improvement seen on the spirogram, steroids).

Thoracotomy showed an anaplastic adenocarcinoma without evidence of metastasis to the mediastinum, and a left upper lobectomy was done. Because of the severity of obstructive airway disease, it was elected to assist the patient's ventilation during the early postoperative period, and this was continued for the first 48 hours. The patient made a rapid recovery and was discharged from the hospital two weeks postthoracotomy.

Spirometry and an arterial blood gas study were repeated two months after operation (Tables 1 and 2). There were no significant changes in forced expiratory volume in one second (FEV_1), maximal midexpiratory flow rate (MMF), maximal voluntary ventilation (MVV), PaO_2 and $PaCO_2$ when compared with the preoperative values. At present the patient is 14 months postthoracotomy. There is no increase in exertional dyspnea, and at present no evidence of tumor recurrence.

Discussion

The first good discussion on ventilatory criteria of inoperability was presented by Gaensler et al[1] in 1955. In a group of 460 tuberculous patients treated with various surgical procedures, 12 of the 13 postoperative deaths due to respiratory insufficiency occurred in patients with a maximal breathing capacity (MBC; now known as maximal

voluntary ventilation—MVV) of less than 50 percent of predicted. Approximately one half of their patients with preoperative MBC's of less than 50 percent of predicted died.

Another major contribution in the evaluation of predictive factors of postoperative difficulty is the study by Mittman[2] which was published in 1961. He stated that the best test for predicting complications was an MBC of less than 50 percent of predicted. The next best indicator of postoperative difficulty was abnormal findings on an electrocardiogram (EKG). This study suggested that the value of multiple tests in predicting operative risk was greater than any single test. By applying a combination of tests (for example, roentgenogram of the chest, MBC, EKG) Mittman was able retrospectively to identify all 28 patients who died of cardiorespiratory failure following operation. However, if all patients in his series identified by this schema had been denied operation, 69 patients who had an uneventful postoperative course would have lost the opportunity for a potentially curative procedure.

In a discussion on the evaluation of pulmonary impairment in surgical patients, R. Drew Miller[3] stated that pneumonectomy would carry a high risk if the MBC was less than 55 percent of predicted, and that lobectomy would carry a high risk if the MBC was less than 40 percent of predicted.

Several groups have looked at pulmonary artery pressure to help determine a patient's capability to tolerate lung resection. Pecora et al[4] studied 176 patients before chest operation. If the resting mean pulmonary artery pressure was 36 to 40 cm of water (26 to 29 mm of mercury), the postoperative mortality was 20 percent. If this pressure was greater than 40 cm of water, there was a 67 percent mortality. However, if the pressure was less than 36 cm of water, there was only a 3 percent mortality.

In an evaluation of risk from pneumonectomy, Van Nostrand et al[5] did not feel that pulmonary artery pressure before and after ligation of the artery to the lung to be resected was of value in predicting postoperative difficulty. However, they did have a 33 percent mortality if the mean pulmonary artery pressure rose to greater than 33 mm of mercury after ligation of the pulmonary artery to the diseased lung. It should be noted that patients in their institution were not selected for pneumonectomy if the mean pulmonary artery pressure increased to more than 40 mm of mercury with ligation. So, many patients with severe disease were not included in the study. They also concluded that the MBC, FVC and FEV_1 did not help to select patients who would have an increased postoperative mortality. As a rule, pneumonectomy was also ruled out in their patients if they could not climb one flight of stairs (19 steps) without severe dyspnea.

Semb et al[6] stated that lung resection should be done with caution in the presence of latent pulmonary hypertension (for example, systolic pulmonary artery pressure of less than 30 mm of mercury, increasing to greater than 50 mm of mercury on exercise). They also stated that lung resection should be avoided if pulmonary hypertension is present.

Uggla[7] found that a resting mean pulmonary artery pressure of 22 mm of mercury was a poor prognostic sign indicating the presence of resting pulmonary hypertension. If the pulmonary artery to the diseased lung was occluded and the pulmonary artery pressure rose sharply or the arterial oxygen tension dropped with exercise, these were bad prognostic indicators.

Karliner et al,[8] in a study of patients undergoing pneumonectomy for carcinoma of the lung, pointed out the value of an elevated arterial carbon dioxide tension (greater than 45 mm of mercury) as an indicator of increased surgical risk. The only one of their 26 patients to suffer postoperative respiratory failure was a patient with an elevated preoperative $PaCO_2$.

Reichel[9] stated that, in his opinion, an exercise tolerance test was the best study to indicate increased risk of postoperative morbidity and mortality. No patient who completed their standard exercise tolerance test experienced cardiorespiratory difficulty postpneumonectomy. However, eight of the 14 patients who were unable to complete the exercise tolerance study experienced serious cardiorespiratory complications. This study suggested that age; abnormal findings on an electrocardiogram and tests of arterial blood gases, lung volumes, flow rates, diffusing capacity and helium mixing time were of no value as predictive indicators of postoperative problems. However, every patient was not studied with this complete battery of tests. Hypercapnia and cardiac decompensation were stated to be relative contraindications to pneumonectomy. In addition, some patients with severe pulmonary disease were rejected for pneumonectomy and so were not included in the study. One, therefore, must be careful in evaluating multiple factors as predictive indicators

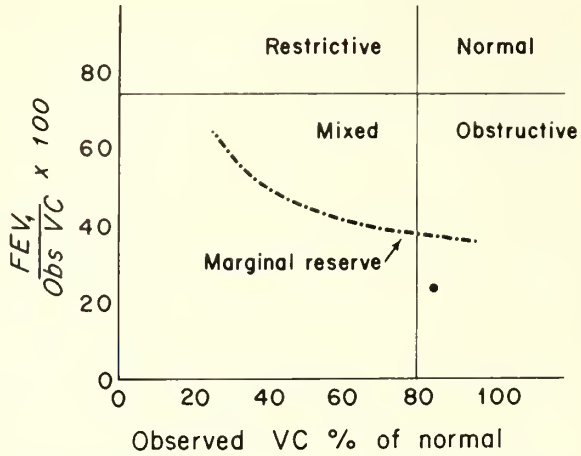

Figure 2.—A four-quadrant diagram plot using the data from the patient presented in the case report demonstrates that this patient has a high risk of postoperative respiratory complications. Since the point falls below the marginal reserve line, assisted ventilation would be indicated in the early postoperative period.

if every patient is not evaluated with all the factors, and when certain patients are preselected out of the study because of the severity of cardiac or respiratory disease.

A report by Larson et al[10] points out the confusion which exists regarding evaluation before thoracotomy. In a study of 533 patients with lung cancer they evaluated such factors as chronic pulmonary disease, cardiovascular disease, other associated serious illness, MBC and vital capacity. They concluded that no significant differences could be found in postoperative morbidity and mortality after evaluating these factors singly or in combination.

In 1956, William F. Miller et al[11] plotted the 0.5 second expiratory capacity × 100/total vital capacity (now known as FEV 0.5 × 100/FVC) versus the total vital capacity (FVC) as percent of normal. This is commonly known as the four-quadrant diagram. Redding et al[12] modified this diagram by plotting $FEV_1 \times 100/FVC$ versus FVC as percent of normal. A "marginal reserve line" was then established on this four-quadrant diagram, and the authors suggested that assisted ventilation would be indicated for any patient whose values fell on or below this dotted line (Figure 2). This diagram should only be used as another indicator of potential postoperative respiratory failure, and should not be used to preclude surgical operation. It should be noted from Figure 2 that data from the patient presented in the case history fell below the marginal reserve line, and yet with temporary assisted ventilation the postoperative course was uneventful.

With the exception of pulmonary artery pressure measurements following unilateral pulmonary artery occlusion, the tests mentioned so far measure overall cardiopulmonary function. The advantage of being able to estimate function in the remaining lung following resection is obvious. Bronchospirometry using a Carlens double lumen tracheal catheter has been used to do unilateral pulmonary function tests. Neuhaus et al[13] used bronchospirometry to predict postoperative MBC. They multiplied the preoperative MBC, as percent of predicted, by the measured percent of vital capacity (VC) contributed by the uninvolved lung. This resulted in a predicted postpneumonectomy MBC, expressed as percent of the predicted normal, with an accuracy which was clinically very satisfactory.

Development of a technique for estimating selective pulmonary function which would be less invasive than either bronchospirometry or right heart catheterization has definite advantages. The radioactive gas Xenon-133 is being used with increasing frequency to evaluate distribution of ventilation and perfusion in the lungs. Kristersson et al[14] described the value of Xenon radiospirometry in predicting pulmonary function loss due to pneumonectomy. He multiplied the preoperative vital capacity by the percent of vital capacity contributed by the noninvolved lung, as determined by Xenon radiospirometry. The FEV_1 was predicted using the same formula. The prediction of postoperative VC and FEV_1 correlated closely with the values obtained in their patients one to twelve months postoperatively. They felt that surgical procedures should not be undertaken if the predicted postoperative FEV_1 was one liter or less.

Olsen et al[15] took the following approach in evaluation for pneumonectomy. Split function testing was recommended if the FVC was less than 50 percent of predicted, the FEV_1 was less than 2 liters, the FEV_1 was less than 50 percent of the FVC, the MBC was less than 50 percent of predicted, the residual volume/total lung capacity (RV/TLC) ratio was greater than 50 percent, the diffusing capacity was less than 50 percent of predicted, or the $PaCO_2$ was greater than 45 mm of mercury. The following methods for split pulmonary function testing were compared. Pulmonary artery pressure during exercise with balloon occlusion of the pulmonary artery to the involved lung, Xenon radiospirometry, and perfusion lung scan using technetium-99m (ferric hydroxide).

TABLE 3.—*Indicators of High Risk of Postoperative Cardiorespiratory Complications*

1. MVV <50% of predicted
2. $PaCO_2$ >45 mm Hg
3. FEV_1 <0.5 L
4. MMF <0.6 L/sec
5. MEFR <100 L/min
6. VC <1.0 L
7. PaO_2 <55 mm Hg
8. Abnormal EKG
9. Failure of improvement in the foregoing values for MVV, FEV_1, MEFR and VC after bronchodilator
10. Grossly abnormal Xenon $\dot{V}/\dot{Q}$ scan

The authors felt that the perfusion lung scan was as reliable as Xenon radiospirometry in assessing individual lung function. The predicted postoperative FEV_1 was obtained by multiplying preoperative FEV_1 in liters by the percent of perfusion to the uninvolved lung.[16] The patient was rejected for surgical operation if the predicted postoperative FEV_1 was less than 0.8 liters, a pulmonary artery pressure of 35 mm of mercury or greater during exercise with balloon occlusion of the pulmonary artery to the involved lung was observed and a PaO_2 of 45 mm of mercury or below occurred during the period of exercise with balloon occlusion of the pulmonary artery. If only two of these three indicators of inoperability were present, pneumonectomy was still undertaken. The three split lung function procedures were administered to 53 patients. Of these 53, five patients were rejected when they failed all three criteria. Of the 28 who passed one or more of the criteria and underwent surgical operation, six (21 percent) died. It should be again noted that many patients underwent a potentially curative resection who would have been denied operation on the basis of many of the criteria reviewed in this paper.

Hodgkin et al[17] in 1973 presented a list of factors which, if present, indicate that a patient has a high risk of postoperative cardiopulmonary complications developing (Table 3). This list applies also to patients who are to have an abdominal operation, as the presence of respiratory or cardiac impairment increases the risk of complications following operation on the abdomen. The presence of one or more of these factors should alert one to potential problems.

Most physicians would agree that the development of postoperative complications may be lessened if pulmonary dysfunction is recognized, evaluated and treated before operation. In any patient with signs or symptoms of pulmonary disease, a spirogram, arterial blood gas study and electrocardiogram should be made routinely as part of the preoperative evaluation. The physician must, in addition, try to determine whether the patient will suffer intolerable cardiorespiratory insufficiency if lung resection is accomplished. A respiratory care program should be initiated preoperatively in these patients in order to attain the best cardiorespiratory function possible. If any of the high risk indicators listed in Table 3 are present in a patient, split pulmonary function should be done. Xenon radiospirometry is preferable to bronchospirometry and right heart catheterization with pulmonary artery pressure measurements because of its noninvasiveness. Resection should not be undertaken if the predicted postoperative FEV_1 is less than 0.8 liter, the $PaCO_2$ is greater than 45 mm of mercury, or if comparative Xenon scans show poor $\dot{V}/\dot{Q}$ matchup in what would be the remaining lung after resection (for example, if the best matching of ventilation and perfusion is in the lung tissue to be removed).

It is to be hoped that by following this approach to evaluation before thoracotomy, one can avoid the all-too-common discovery in the postoperative period that the patient is now a cardiorespiratory cripple.

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Vascular Manifestations of von Recklinghausen's Disease

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A causal relationship between von Recklinghausen's disease, or neurofibromatosis, and arteriolar abnormalities has been reported in the European literature. A patient was seen who had biopsy-proved neurofibromatosis and renovascular hypertension and retroperitoneal bleeding. An arteriographic study showed multiple small aneurysms throughout the coeliac axis, the superior mesenteric artery and in several small intrarenal vessels. Renal vein renin levels were elevated particularly in the right renal vein, supporting the diagnosis of renovascular hypertension. Both the aneurysms seen in angiographic studies and the retroperitoneal hemorrhage are probably vascular manifestations of von Recklinghausen's disease. Support for this conclusion is enhanced by the absence of clinical, laboratory or histologic data supporting the only tenable differential diagnosis, periarteritis nodosa.

In 1882, at a meeting in honor of the 25th anniversary of the Berlin Institute of Pathology, von Recklinghausen described the neuroectodermal syndrome that bears his name.[1] Neurofibromatosis, or von Recklinghausen's disease, is a congenital hereditary disease characterized by pigmented skin lesions, the so-called café-au-lait spots, cutaneous neurofibromas, tumors of the central and peripheral nervous system and multiple skeletal abnormalities (including scoliosis, local gigantism, subperiosteal bone cysts and tibial pseudoarthrosis). Mental retardation is commonly present. Pheochromocytoma occurs infrequently and is nevertheless a well-known, clinical concomitant of von Recklinghausen's disease.

Although the vascular abnormalities that occur in von Recklinghausen's disease have been described in the European literature,[2-6] the descriptions have not received wide attention in English. The pathologic changes that occur in small-to-medium-sized arteries in patients with neurofibromatosis can be similar to those in patients wth perarteritis nodosa,[3-6] with both luminal obliteration and microaneurysm formation.[7,8] A patient with retroperitoneal bleeding and renovascular hypertension probably secondary to the vascular lesions of von Recklinghausen's disease is reported here. However, although it has never been reported in the literature, we cannot completely ex-

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clude the simultaneous occurrence of neurofibromatosis and periarteritis nodosa in the same patient.

Report of a Case

A 38-year-old Caucasian man was admitted to the emergency room at San Francisco General Hospital on January 31, 1974 because of sudden onset of pain in the right lower quadrant of the abdomen and right flank, as well as nausea and vomiting earlier in the day. The pain was sharp and jabbing at first and then progressed to a dull steady ache. The patient had not had fever, chills, arthralgias, myalgias, rashes, diarrhea, constipation, dysuria, hematuria or pyuria, but malaise and lethargy had been present for approximately one month.

The medical history was significant in that the patient had a life-long history of café-au-lait spots and multiple subcutaneous soft tissue tumors. His mother had large numbers of café-au-lait spots and subcutaneous tumors, and because of her "bumps and spots," was often referred to by her children as "the toad lady." The patient had no allergies, and salicylates for malaise and lethargy were the only medications ingested. He reported having smoked two to three packages of cigarettes a day since the age of nine years. Review of systems showed a six-month history of increasing shortness of breath and dyspnea on exertion, associated with a mild productive cough, but no history of asthma.

On physical examination, the patient was found to be asthenic and in moderate respiratory distress. Blood pressure was 140/75 mm of mercury, pulse 100 beats per minute and temperature 36.2°C (97.2°F). The conjunctivae were clear, and there were no fundic abnormalities. Three petechiae were noted on the hard palate. No abnormal neck masses were seen. Examination of the chest showed a respiratory rate of 25 breaths per minute with the use of accessory muscles, an increased anterior-posterior diameter, hyper-resonance to percussion and a prolonged expiratory phase, but no rales or wheezes. No cardiac abnormalities were detected. Abdominal organs were not enlarged, but there was tenderness in the right lower quadrant of the abdomen with voluntary guarding and rebound in that area. Bowel sounds were normal. There was no costovertebral angle tenderness. No abnormalities were noted on neurologic examination. On examination of the skin, six café-au-lait spots greater than 2 cm in diameter were seen, each with a "coast of California" configuration. There were four subcutaneous nodules, the largest of which was a small firm movable nontender nodule 2 cm in diameter over the left upper quadrant of the abdomen. There was a similar lesion over the right upper quadrant, and a larger soft tumor approximately 8 cm in diameter over the posteromedial aspect of the left leg. Pressure on the leg lesion produced a sensation of numbness and tingling over the medial and plantar aspects of the left foot. Rectal examination showed no abnormalities and the stool was guaiac negative.

Figure 1.—Late arterial phase of selective right renal arteriogram showing capsular branch (white arrows) notably displaced from margin of renal parenchyma. Also shown are aneurysmal dilatations of several small intrarenal branches (black arrows).

Laboratory tests on admission showed a hematocrit of 31 percent and a leukocyte count of 30,000 per cu mm. Results of urinalysis were as follows: specific gravity 1.020, hydrogen ion concentration (pH) 6.0, protein 2+ and leukocyte count 10 to 15 per high power field; no red cells or red cell casts were present. Serum electrolytes, calcium, phosphorus, bilirubin, liver enzymes and amylase were within normal limits and creatinine was 1.2 mg per 100 ml and blood urea nitrogen 21 mg per 100 ml. Arterial blood gases on room air showed a pH of 7.53 with a carbon dioxide pressure (pCO_2) of 26 and a partial pressure of oxygen (pO_2) of 56. The albumin to globulin ratio was 2.9/3.1. A roentgenogram of the chest showed bibasilar fibrosis with apical bullous disease. An

Figure 2.—Arterial phase of coeliac arteriogram showing aneurysms of small splenic (open arrow) and hepatic (closed arrows) branches.

Figure 3.—Arterial phase of superior mesenteric arteriogram showing multiple aneurysms (black arrows).

electrocardiogram showed a sinus tachycardia but no other abnormalities.

On exploratory laparotomy, done on February 1, 1974, a large right-sided retroperitoneal hematoma was seen, extending from behind the liver to the base of the small bowel mesentery and involving the perinephric area. No bleeding sites or aneurysms were found. Postoperative angiographic studies to identify a bleeding site showed no occlusive disease of either main renal artery; however, vascular irregularities and aneurysmal dilatations were seen in the small vessels of the right kidney. There was pronounced lateral displacement of a capsular branch of the right renal artery (Figure 1) and multiple small aneurysms were present throughout the distribution of the coeliac axis (Figure 2) and the superior mesenteric artery (Figure 3). Although no active bleeding site was identified, the retroperitoneal hematoma probably resulted from a right renal subcapsular hemorrhage that ruptured into the retroperitoneum.

Postoperatively, hypertension developed with blood pressures ranging from 180/120 to 230/130 mm of mercury, but it was easily controlled with methyldopa (250 mg administered orally three times a day), hydrochlorothiazide (50 mg administered orally four times a day) and spironolactone (25 mg administered orally three times a day). The leukocyte count fell to 6,800 per cu mm with a normal differential. Peripheral eosinophilia was not present; total eosinophil counts were 280 and 290 per cu mm on two determinations. The hematocrit was 38 percent, reticulocyte count 0.7 percent, and platelet count 175,000 per cu mm. Results of urinalysis were within normal limits; no red cell casts were seen on microscopic examination. Serum electrolytes, glucose, creatinine, blood urea nitrogen and liver function tests all gave normal results. Albumin/globulin ratio rose to 4.4/3.2. Sedimentation rate was elevated to 40 mm per hour. Result of a Venereal Disease Research Laboratories (VDRL) test was weakly reactive, but results of a fluorescent treponemal antibody-antigen absorption test were negative. Anti-nuclear antibody, lupus erythematosis cell preparation, rheumatoid factor and hepatitis-associated antigen tests all gave negative results. Serum protein electrophoresis showed slight increases in α^1, α^2, and β globulins.

On renal scan, slight asymmetry of renal function was noted, reflecting decreased clearance by the right kidney. Results of an upper gastrointesti-

nal series showed no abnormalities except for a hiatus hernia. No abnormalities were seen in roentgenograms of the skull. Examination of a testicular biopsy specimen showed no abnormalities and no signs of arteritis. Two subcutaneous nodules were excised; one was a lipoma and one a neurofibroma, characterized by whorls of spindle-shaped cells with oval nuclei and eosinophilic cytoplasm (Figure 4). Neural elements were discernible in the tumor substance. Pulmonary function studies showed pronounced obstructive pulmonary disease with decreased diffusion capacity. The urinary level of vanillymandelic acid (VMA) during low VMA diet with no hypotensive medicines was 3.9 μg per ml (normal range, 0.5 to 7.5). Renal vein renin studies done while no thiazides or other hypotensive agents were being administered and while the patient had been continuously supine for 12 hours showed notable elevation of renin in the inferior vena cava and both renal veins. A difference between the level at the right renal vein orifice (133.1 ng per ml in three hours) and the left renal vein (72.1 ng per ml in three hours) and inferior vena cava (80.9 ng per ml in three hours) suggested asymmetric renal release with right renal predominance. The pronounced elevation of renin (normal range, 2 to 10 ng per ml in three hours) in the absence of malignant hypertension suggested a renovascular cause for the hypertension.

The patient was discharged on February 24, 1974 and no complications have occurred (four months after admission). Since discharge the patient has felt well. Hypertension is well controlled by the antihypertensive regimen instituted. Malaise and lethargy have disappeared, and the patient has gained 1.4 kg (3 lb). There are no signs of active vasculitis, but the erythrocyte sedimentation rate remains elevated.

Discussion

The diagnosis of von Recklinghausen's disease in our patient was based on the strong family history and on the presence of café-au-lait spots and biopsy-proved neurofibromas. In addition, there were several findings in the patient that, at first glance, were unexplainable by that diagnosis. First, there was retroperitoneal hemorrhage. Second, coeliac and superior mesenteric arteriograms showed multiple diffuse aneurysmal dilatations of small to medium-sized arteries characteristic of periarteritis nodosa.[9-14] Third, renal arteriograms showed lateral displacement of the right renal capsular artery, suggesting that the retroperitoneal hematoma developed following a perinephric hemorrhage. Fourth, hypertension developed postoperatively with a normal urinary VMA level and high renal renin levels. Despite these unusual features, we believe that neurofibromatosis was the best single unifying diagnosis for our patient.

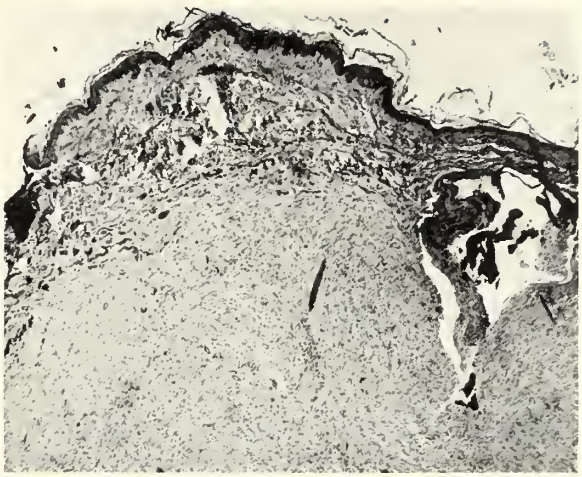

Figure 4.—Superficial neurofibroma of the skin. In this low power view the tumor is protruding into the dermis and elevating the epidermis. The tumor nuclei are elongated and serpentine.

The major differential diagnosis, of course, was periarteritis nodosa. The pathologic features of periarteritis are fibrinoid necrosis of the intima and media of small to medium-sized arteries, associated with a pleomorphic perivascular inflammatory reaction, often rich in eosinophilic leukocytes.[15-17] Giant or epithelioid cells with perivascular granuloma formation are often present. Aneurysms develop following fibrinoid necrosis of the smooth muscle and elastic tissue within the vessel wall. Narrowing of the vessel lumen may be owing to thrombosis in an aneurysm, intimal proliferation or reparative fibrosis and scarring. The frequency with which the aneurysms can be documented radiographically is unclear, but Bron and Gajaraj[10] suggested that in 60 percent of their patients with periarteritis nodosa, there were angiographically detectable aneurysms. It may be difficult to detect them in a given patient since the disappearance of angiographic evidence of aneurysms has been described[18] during both spontaneous and therapeutic remissions. When aneurysms are seen, the radiographic appearance is considered so characteristic that Cabal and Holtz[11] stated confidently that "if multiple small aneurysms are demonstrable, this is considered virtually diagnostic" (of periarteritis nodosa).

It is known that von Recklinghausen's disease can also involve the vascular tree. Cabal and Holtz[11] maintained that "vascular changes secondary to neurofibromatosis involve larger arteries and are usually extraparenchymal." Indeed, of the eleven patients with vascular neurofibromatosis described by Halpern and Currarino[19] and Cornell and Kirkendall,[20] there were abdominal aortic coarctations in five and stenosis of the renal arteries in ten, with or without aneurysm formation. However, Reubi[5] found pronounced changes in the small arteries (50 μ to 1.0 mm) of six patients with neurofibromatosis. He was able to distinguish three kinds of vascular abnormality, depending on the size of the involved vessel.[5,6] Arterioles between 50 and 400 μ in diameter showed intimal proliferation with luminal obliteration. Periarterial nodules developed around vessels that were 100 to 700 μ in diameter. The nodules, which were composed of fusiform cells, often extended from the adventitia down to the intima. Arteries 0.5 to 1.0 mm in diameter had a fibrohyaline thickening of the intima with disruption of both the muscularis and the elastic tissue of the media, leading to aneurysm formation.

Reubi believed that the vascular lesions of von Recklinghausen's disease could be distinguished from those of periarteritis nodosa by the absence of perivascular inflammation and the lack of tissue necrosis. Feyrter[2] also described the vascular abnormalities associated with neurofibromatosis. His descriptions of intimal proliferation, perivascular nodule formation and intimal and medial hyaline deposition with aneurysmal dilatation are quite similar to those of Reubi.

The incidence of vascular involvement in von Recklinghausen's disease is unknown but Khalatbary,[3] in an exhaustive review of the foreign literature, found 44 cases of vascular neurofibromatosis reported before 1959. Halpern and Currarino,[19] in their 1965 review of neurofibromatosis with renovascular hypertension, reported four more cases with small vessel lesions similar to those described by Reubi. Brasfield and Das Gupta[21] stated that in four of their 110 patients there was "vascular involvement," but they did not characterize the lesions they found.

After reviewing these pathologic descriptions of vascular neurofibromatosis, we believe that the multiple aneurysms shown in our patient's visceral circulation by angiography reflected the aneurysmal dilatations of von Recklinghausen's disease rather than the lesions of periarteritis nodosa.

On admission retroperitoneal and perirenal hemorrhage was noted in our patient. Although several cases of visceral neurofibromatosis complicated by gastrointestinal hemorrhage have been reported,[22-24] no cases of perirenal hemorrhage have appeared in the literature to date. In the case reported by Davidson,[22] the intestinal bleeding originated from large veins coursing submucosally as they drained an extremely vascular jejunal tumor. Grill and Kuzma[23] also described a very vascular tumor, with bleeding from multiple sites where tumor sinusoids had perforated through ileal mucosa. In their review of the literature they found only 16 cases of small bowel neurofibromatosis, of which there were only five with symptoms referable to the gastrointestinal tract. Clinical findings included vague abdominal discomfort, gastrointestinal bleeding and bowel obstruction. In no instance was retroperitoneal bleeding described.

Perirenal hemorrhage is a well-described complication of periarteritis nodosa.[25-29] Presumably, the hemorrhage that occurs in periarteritis nodosa results from perivascular inflammation with necrosis and then rupture of the vessel wall.[11] Since we know that the vascular lesion in neurofibromatosis leads to disruption and atrophy of the vessel wall, it is reasonable to assume that involved vessels would be subject to rupture and hemorrhage, just as in periarteritis nodosa. The stimulus for rupture might be insignificant trauma or even the vascular stress of worsening hypertension. In any event, it is certainly conceivable that in our patient there was bleeding from the rupture of a small vessel aneurysm of the type occurring in patients with neurofibromatosis.

Our patient has been hypertensive since laparotomy. Hypertension is a common complication of periarteritis, occurring in approximately 50 percent of cases.[16,30,31] Frohnert and Sheps,[32] in a long-term evaluation of steroid therapy in periarteritis, found that hypertension eventually developed in 37 of their 130 patients. Hypertension, of course, is also described in von Recklinghausen's disease. The association of neurofibromatosis and pheochromocytoma has been widely publicized. In fact, it has been estimated that from 5 to 25 percent of all reported pheochromocytomas have been found in patients with von Recklinghausen's disease.[33,34] Brasfield and Das Gupta,[21] however, found only one pheochromocytoma in 130 patients with neurofibromatosis.

Our patient had a normal 24-hour urinary level

of VMA while on a low VMA diet and off all antihypertensive medicines. Renovascular hypertension has also been described in von Recklinghausen's disease. In previously reported cases peripheral renin levels[20] or angiotensin assays[19] were within the normal range. In our patient, there were notably elevated renin levels in the renal vein and inferior vena cava. In the supine position, the renin level in the right renal vein was much higher than the left, with a step-down between the right renal vein and the inferior vena cava. These findings strongly suggested that the patient's hypertension was renovascular in origin, with the right kidney being the major source of the elevated renin levels. Although all of the cases of renovascular hypertension with neurofibromatosis reported by Halpern and Currarino,[19] Cornell and Kirkendall,[20] and Bloor and Williams[35] had large vessel disease with stenosis and aneurysm formation of the aorta or the renal arteries or both, hypertension was also commonly found in the patients with small- to medium-sized vessel involvement described in the European literature.[3,5,6]

In our patient, chronic obstructive pulmonary disease was determined by clinical, radiologic and laboratory criteria. Presumably, the lung disease was related to a smoking history of 800 packages of cigarettes a year. Although pulmonary involvement, including acute and chronic infection, asthma, diffuse interstitial fibrosis, bronchiectasis, parenchymal granulomas with and without caseous necrosis and pulmonary infarction, has been well documented in 12 to 47 percent of patients with periarteritis nodosa,[16,30,31] a diagnosis of pulmonary periarteritis nodosa in our patient was opposed by the absence of peripheral eosinophilia. Eosinophilia, often with counts up to 1,500 per cu mm, occurs in 70 percent of patients with periarteritis with lung involvement. Pulmonary involvement in von Recklinghausen's disease is uncommon. The most frequently described thoracic manifestations of von Recklinghausen's disease are neurogenic tumors of the mediastinum, chest wall and pleura.[36] Bronchial and pulmonary neuropenic tumors do occur but are extremely rare. Of importance to our hypothesis is the case reported by Israel-Asselain,[37] who described diffuse interstitial fibrosis of the reticulonodular type in a mother and son, both of whom had neurofibromatosis.

Our patient presents a diagnostic and, therefore, therapeutic dilemma. Although the perinephric hemorrhage, the renovascular hypertension and the angiographic evidence of multiple microaneurysms throughout the visceral circulation all suggested the diagnosis of periarteritis nodosa, we believe that the absence of fever, skin rashes, arthralgias, myalgias or weight loss, as well as the normal testicular biopsy specimen, the absence of peripheral eosinophilia, the normal results of urinalysis and the benign postoperative course make that diagnosis unlikely. Moreover, the patient definitely had neurofibromatosis, a disease known to cause renovascular hypertension and to lead to microaneurysm formation in the same small- to medium-sized arteries affected in periarteritis nodosa. We suggest that both the aneurysms seen on angiography and the retroperitoneal hemorrhage are vascular manifestations of von Recklinghausen's disease. Although at present we cannot absolutely exclude periarteritis nodosa in our patient, we believe that a single unifying diagnosis is appropriate and that all the clinical features reflect the complications of von Recklinghausen's disease. As a consequence we have elected to withhold steroid therapy.

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Flexible Fiberoptic Bronchoscopy

Anesthesia, Technique and Results

EDMUNDO YRIGOYEN, MD, *and* Y. F. FUJIKAWA, MD, *Long Beach*

During a period of three years, 256 diagnostic bronchoscopies were done with flexible fiberoptic bronchoscopes at a Veterans Administration hospital. In all of these procedures, topical cocaine hydrochloride anesthesia was used, and it proved satisfactory and free of any undesirable side effects.

The peroral route using an endotracheal tube is preferred for flexible bronchofiberscopy. Fluoroscopic guidance is essential in examining peripheral lung lesions. A 70 percent positive yield was obtained for patients with peripheral carcinoma of the lung as contrasted to a 47 percent yield when the tissue specimens were obtained blindly.

THE FLEXIBLE BRONCHOFIBERSCOPE has considerable advantages over the limitations of the rigid bronchoscope[1,2] in the diagnosis of peripheral lung lesions[3-9] and has largely replaced the rigid scope since its introduction by Ikeda in 1968. Many of those who use a flexible bronchofiberscope prefer the transnasal route using lidocaine as the topical anesthetic. We propose to re-evaluate the use of cocaine hydrochloride as a topical anesthetic, the advantages of using an endotracheal tube and our results with the flexible bronchofiberscope in the diagnosis of peripheral malignant lesions of the lung.

Materials and Methods

We have been using both the 5 mm and 6 mm Machida bronchofiberscopes. The 5 mm model has an upward deflection of 180 degrees and the downward deflection of 10 degrees. In addition, the flexible tip can be rotated or panned 30 degrees to the right or left; this feature being very useful for guiding the instrument into the subsegments or sub-subsegments, especially in the apices. The disadvantages of the 5 mm instrument are that it is quite fragile and its channel is only 1.4 mm in diameter, which precludes obtaining good specimens with the tiny biopsy forceps. The 6 mm instrument also has an upward and downward deflection of 180 and 10 degrees respectively. In most models, the lateral panning has been eliminated, resulting in a sturdier instrument. The 6 mm bronchofiberscope has a 2.2 mm channel so that suctioning is more effective, and adequate biopsy specimens can be obtained with a larger biopsy forceps.

Premedication

In patients with no cardiac, respiratory or liver problems, a barbiturate such as sodium secobarbital (50 to 100 mg) is given approximately an hour and a half before the scheduled time; atropine 0.4 to 0.6 mg and codeine 30 to 60 mg are given hypodermically 45 minutes later. When broncho-

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Submitted, revised, August 22, 1974.

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TABLE 1.—*Results of 206 Consecutive Diagnostic Flexible Bronchoscopies in Patients with Suspected Bronchogenic Carcinoma*

	Positive	Negative	False Negative	Percent of Positive
Peripheral (139)				
with fluoroscopic guidance (93)	28	53	12	70
without fluoroscopic guidance (46)	8	29	9	47
Central (43)	26	7	10	72.2
Normal (8)	0	8	0	..
TOTAL: 190*	62	97	31	66.6

*12 patients had two and 2 patients had three fiberoptic bronchoscopies.

TABLE 2.—*Results of Flexible Fiberoptic Bronchoscopy in 43 Patients with Suspected Lung Tumors After Negative Results from Previous Rigid Bronchoscopy*

	Positive	Negative	False Negative	Percent of Positive
Peripheral (30)				
with fluoroscopic guidance (14)	9	3	2	81.8
without fluoroscopic guidance (16)	6	7	3	66.6
Central (10)	6	1	3	66.6
Normal (3)	0	3	0	..
TOTAL: 43	21	14	8	72.4

fiberscopy is done through a tracheostomy or in an intubated patient, premedication is usually not necessary. In very ill patients, atropine alone may be sufficient.

Topical anesthesia

The anesthetic is administered with the patient sitting or in a high Fowler's position. In a sterile medicine glass, 2 ml of a 10 percent solution of cocaine hydrochloride is placed; 3 ml of a 10 percent cocaine solution is placed in a second medicine glass and this is diluted with saline to make a 2.5 percent solution. A small cotton pledget affixed to a Jackson cross-action forceps is dipped into the 10 percent cocaine solution and any excess solution is removed by pressing the pledget against the side of the glass. The tongue and posterior oropharynx is swabbed once or twice; then, the pledget is placed in each pyriform sinus for 30 to 60 seconds. The patient or an assistant grasps the tongue with gauze and pulls it out as far as possible. The patient is reminded to relax and breathe slowly and deeply. Using a laryngeal mirror, the epiglottis is then swabbed with the 10 percent cocaine solution. Then the diluted 2.5 percent cocaine solution is instilled directly into the larynx in fractions of 1 to 2 ml. With the patient tilted to the left, the left bronchial tree can be anesthetized. The total amount of cocaine rarely exceeds 300 mg. As soon as the cough reflex is abolished, the examination can be done, instilling small fractions of 2.5 percent cocaine through the channel in the scope as necessary.

Procedure for flexible bronchofiberscopy

In most cases, a flexible tube such as a 9 or 9.5 mm cuffed endotracheal tube with a wire guide is introduced by indirect laryngoscopy into the trachea. If, for some technical reason this is not possible, the endotracheal tube is slipped over the bronchoscope as a sleeve. The scope is then introduced directly into the trachea with the patient lying supine, and is passed down to the level of the carina. Then, with the patient breathing deeply, the endotracheal tube is slipped into the trachea during inspiration. A mouthpiece is placed about the endotracheal tube for protection. Oxygen can be given through the 2.2 mm channel or through the sidearm of an attachment such as a Rovenstein elbow or a tracheostomy swivel unit.

In the case of peripheral lesions, the procedure is done under fluoroscopic guidance. The involved segment is predetermined by a careful study of the posteroanterior, lateral roentgenograms and planigrams when available. Ideally, routine bronchograms of the involved area would be most helpful, but this is not yet possible under our present setup. During fluoroscopy, anteroposterior, oblique and lateral views are obtained to determine the exact position of the brush or curette in relation to the lesion.

The diagnosis of peripheral malignant lung lesions

This report does not include any therapeutic bronchofiberscopies or the first fifty cases since we consider these early cases a learning experience.

Table 1 is a breakdown of the location of lesions examined. Peripheral lesions are determined by their location on x-ray films and by showing no evidence of bronchial involvement by direct visualization with the 5 or 6 mm bronchofiberscope. Central lesions are those visible on direct examination. We have had 139 peripheral lesions from which brush biopsy specimens were obtained. Of these, 93 were secured under fluoroscopic guidance with positive cytology for malignancy in 28 out of 40 proven cases of bronchogenic carcinoma, an incidence of 70 percent. Brush biopsies were

done blindly on 46 patients with 47 percent positive findings (eight out of 17 proven cases of bronchogenic carcinoma), clearly demonstrating the superiority of collecting the specimens under fluoroscopic guidance.

Flexible fiberoptic bronchoscopies were done on 43 patients with suspected lung tumors in whom results of previous rigid bronchoscopies had been negative. Thirty-nine of these procedures were done within two weeks, and four within two months of the previous rigid bronchoscopies. As shown in Table 2 we were able to make a positive diagnosis in 21 of 29 patients with bronchogenic carcinoma, a yield of 72.4 percent. Of the 29 cases of bronchogenic carcinoma, 20 were peripheral and a diagnosis was made in 15 of these cases, a positive yield of 81.8 percent under fluoroscopic guidance and 66.6 percent without fluoroscopy. This clearly demonstrates the superiority of the flexible bronchofiberscope over the conventional rigid bronchoscope.

Examples of brushing under fluoroscopic guidance are shown in Figures 1 through 3. The case illustrated in Figure 4 is that of a 42-year-old man who had pulmonary tuberculosis in 1971 and now has residual bilateral upper lobe cavities. The patient reentered the hospital with complaint of blood streaked sputum for three days. Bronchoscopy was done with the 6 mm bronchofiberscope and, to our surprise, on entering the left upper lobe, we were able to get the scope into the large cavitary lesion shown in the spot film. We are not aware of any similar case reported in the literature.

Discussion

Anesthesia

In 1924, a special committee of the American Medical Association chaired by Dr. Emil Mayer reported on toxic effects following the use of topical anesthetics. Of the 43 deaths collected, 26 were due to cocaine. In all of them, convulsions were followed by respiratory arrest within a few minutes. The dosage of cocaine and the total amount employed were not stated for 21 of the 26 patients.[10] Since Mayer's report, the use of cocaine as a topical anesthetic has fallen into disrepute except in a few centers.

Cocaine is normally detoxified by the liver at the rate of one minimal lethal dose (MLD) per hour. The fatal dose has been stated to be about 1.2 grams. The recommended maximal dosage for topical anesthesia is 3.3 mg per kg of body weight, (about 225 mg for a 150 lb adult)[11] and the anesthesia persists for more than 20 minutes.[12] Serious complications arising from topical anesthesia appear to be related to a more rapid than usual absorption of the drugs used (cocaine, lidocaine, tetracaine).[13] This absorption rate depends on the state of the mucosa, amount of mucus in the airways, rate and depth of respiration, state of the patient's circulation, period of time in which the drug is given and the total dose.[14,15] The clearance rate of these drugs is impaired in patients with heart failure or liver disease.[16]

Credle,[17] in a recent review of complications during flexible fiberoptic bronchoscopies in 24,521 collected cases does not mention the use of cocaine topical anesthesia. He reports one death and five serious complications due to tetracaine, which is still used by some. Weisel[18] reported 1,000 consecutive bronchoscopies in which 2 percent tetracaine was used with no fatalities. However, severe reactions occurred in seven patients, in two of whom bronchoscopy was done subsequently without difficulty using 4 percent and 10 percent cocaine solution. Adriani[19] reported 15 deaths due to tetracaine in 1956. At the La Jolla Shores Conference on Flexible Fiberoptic Bronchoscopy held in September 1973, lidocaine was noted to be the most commonly used topical anesthetic agent.

In addition to 256 flexible fiberoptic bronchoscopies, we have done 2,040 rigid bronchoscopies in a seven-year span (February 1967 to February 1974) using topical cocaine anesthesia without any complications requiring treatment. In particular we have seen no convulsions, respiratory depression or cardiac or respiratory arrest. We attribute this to the judicious use of the drug following adequate premedication. We have noted occasional patients with transient moderate hypotension, sinus tachycardia, nausea or euphoria; but none of these required therapy. One of us (Y.F.F.) has used cocaine topical anesthesia in over 4,000 bronchoscopies between January 1944 and January 1967. In the earlier period, a DeVillbiss atomizer was used to spray 10 percent cocaine solution repeatedly into the oral cavity and the posterior pharynx until the gag reflex was eliminated and fractional instillation could be done by indirect laryngoscopy until the cough reflex was abolished. In those earlier days when the amount administered was not well controlled, an occasional toxic reaction was observed in which the

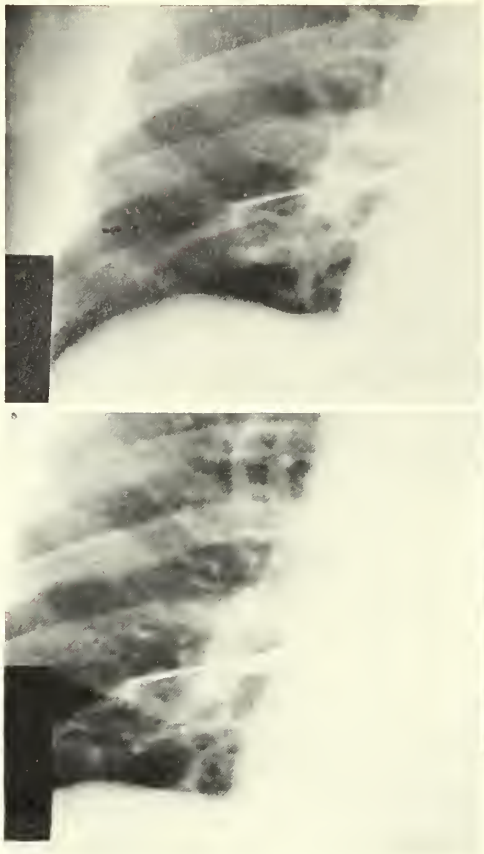

Figure 1.—Small coin lesions are also amenable to brush biopsy.

Figure 2.—54-year-old man with recent blood streaked sputum and a right upper lobe infiltrate. Bush biopsy: adenocarcinoma.

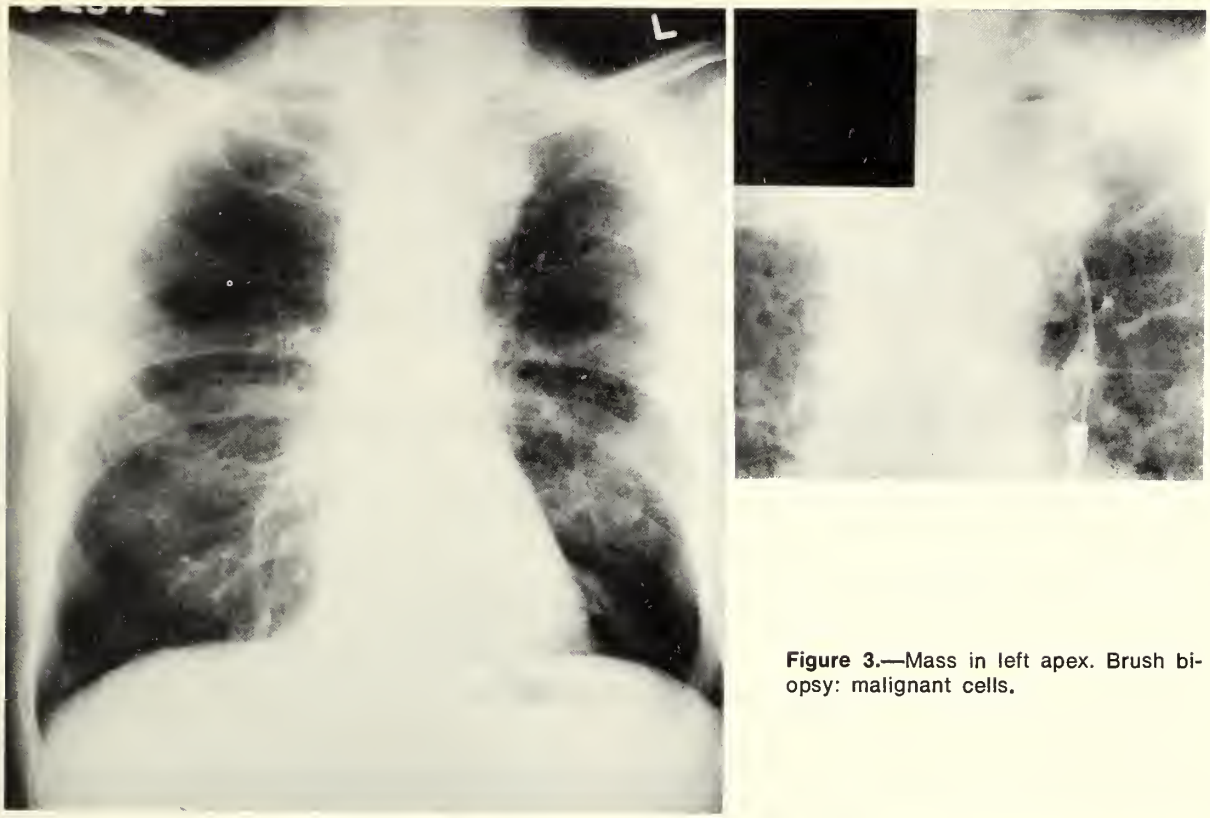

Figure 3.—Mass in left apex. Brush biopsy: malignant cells.

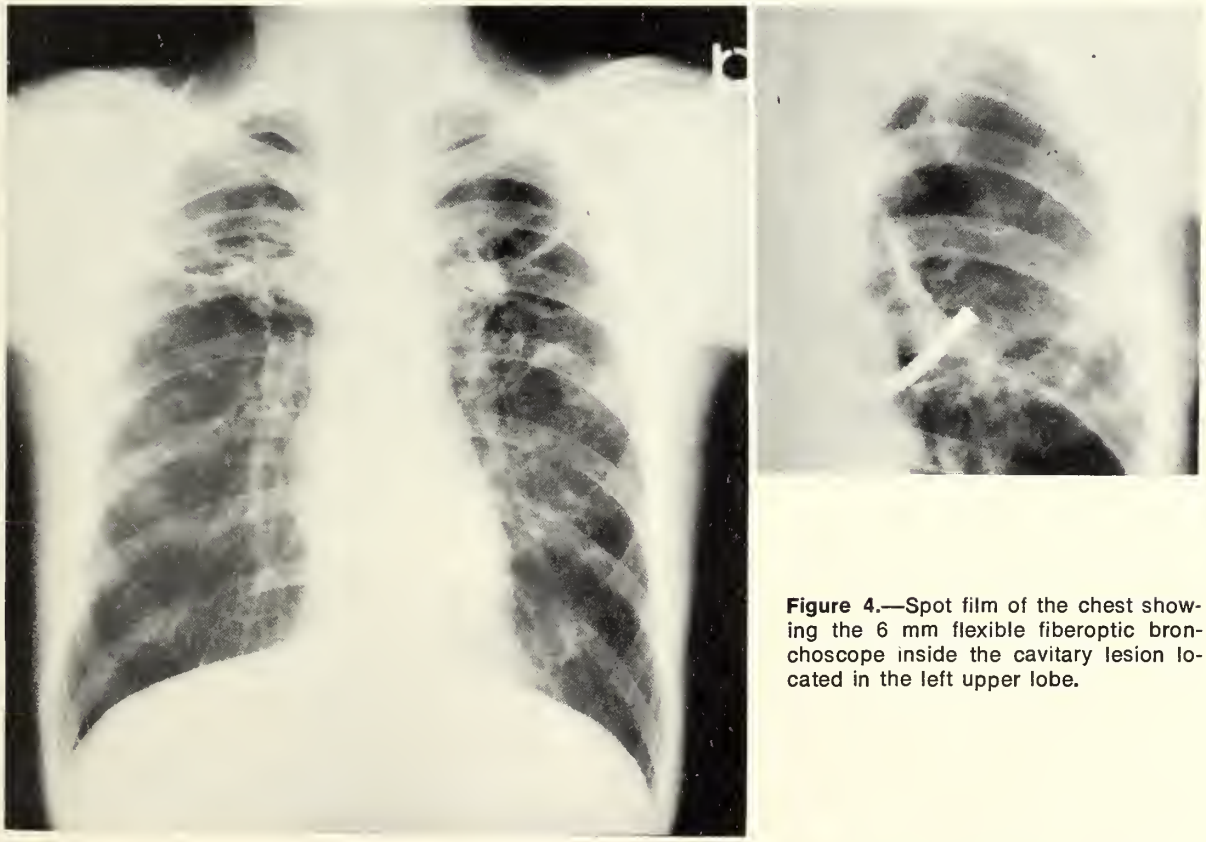

Figure 4.—Spot film of the chest showing the 6 mm flexible fiberoptic bronchoscope inside the cavitary lesion located in the left upper lobe.

patients became extremely restless and began jerking intermittently. These responses were quickly controlled by intravenous administration of a barbiturate such as sodium pentothal or sodium amobarbital with no fatalities.

A barbiturate such as sodium secobarbital or, more recently, diazepam[20] may be given as a premedication since they may be valuable in protecting against cocaine induced seizures.

Endotracheal tube

If an adequate topical anesthetic has been administered, the endotracheal tube can be passed either by indirect laryngoscopy or by the method mentioned previously quite easily. The patients tolerate this with little or no discomfort. The endotracheal tube is routinely used even for bedside bronchofiberscopy. Good topical anesthesia is the key to successful intubation.

The advantages of using an endotracheal tube are many:

- It facilitates repeated removal and reinsertion of the bronchofiberscope for suction and introduction of brushes, curettes or biopsy forceps.
- It probably minimizes or prevents contamination of the bronchial tree by nasopharyngeal secretions.
- Very ill patients can be bronchoscoped without interruption of their ventilatory support.
- For excessive secretions or moderate hemorrhage, a suction tube can be introduced to keep the airway clear.
- In the event of severe hemorrhage, the scope would be introduced into the nonbleeding bronchus and the endotracheal tube advanced into that bronchus, thereby assuring an adequate airway to that lung. In such instances, the cuff can be inflated and the patient placed on his side with the bleeding site dependent. The patient can be placed in the Trendelenburg position in order to drain the blood, at the same time delivering oxygen to the good lung until the situation has resolved.[21] Although we have not had to resort to this tactic, with an endotracheal tube in place, we are prepared for such emergencies.

Results

This limited study reveals the safety of cocaine topical anesthesia when used as described above. The advantage of using the fluoroscopic image intensifier for peripheral lesions as well as the advantage of the flexible fiberoptic bronchoscope over the conventional rigid bronchoscope in diagnosing lung cancer is clearly evident.

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Screening for Skin Cancer at a County Fair

E. DORINDA LOEFFEL, MD, *Chicago,* and WILLIAM WATSON, MD, *Stanford*

Six skin cancer detection clinics were held at a county fair booth in Turlock, California during August, 1973. Examination of sun-exposed skin areas in 605 people showed potential skin cancer in 28.6 percent of people 25 years of age or older. Of the people examined, 135 were referred to their own physicians for follow-up diagnosis and treatment of skin lesions.

EARLY RECOGNITION and successful treatment of skin cancer is a realistic goal, given the visibility of early malignant skin lesions and the ease of rapid diagnostic confirmation through skin biopsy. Diagnostic delay of the "sore that won't heal" seems inexcusable, but understandable, due to lack of pain coupled with cosmetic indifference, personal neglect and fear of going to a physician's office. General ignorance about skin cancer, transportation problems for geriatric patients and lack of convenient health care facilities also probably contribute to delay in diagnosis.

To counteract such difficulties, efforts have been made in several areas of the country to "reach" people by taking cancer-detection units to unusual places. In Nebraska, a mobile house trailer with special examination rooms and x-ray equipment is used in screening geriatric patients for skin cancer as well as cancer of the mouth, larynx, breast, lung, uterus and colon.[1] In Virginia, several Saturday clinics have been held in rural areas for detection of skin and oral cancer among farmers.[2] In North Carolina, a skin cancer detection clinic was operated at the 1972 State Fair, with special emphasis on educating large numbers of people about the dangers to skin of excessive sunlight exposure.[3] Most of these programs have depended on physician volunteers, along with promotional, organizational and financial support from the American Cancer Society.

In August, 1973, a pilot skin cancer screening booth sponsored by the American Cancer Society and the National Program for Dermatology was operated for six days at the Stanislaus County Fair in Turlock, California. Turlock is a community of 14,000 people located in the hot, fertile San Joaquin Valley and serving a surrounding population of farmers and ranchers at very high risk for developing skin cancer. An estimated 50,000 people attend the fair at Turlock every year, so that detection of a large number of people with skin cancer could be anticipated if visitors to the fair could be persuaded to undergo skin examinations.

Attention was drawn to the booth in advance through newspaper articles and contact with the Stanislaus County Medical Society. Posters, pamphlets and an audiovisual program about cancer detection helped to advertise the location of the booth. Cancer Society volunteers giving friendly reassurance that examinations were quick, free and painless helped popularize the booth.

Skin examinations were done by five physicians from the Stanford University Dermatology De-

From the Department of Dermatology, Stanford University Medical Center, Stanford.

Submitted July 9, 1974.

Reprint requests to: W. Watson, MD, Department of Dermatology, Stanford University Medical Center, Stanford, CA 94305.

Date_____

Name_____
Last First middle initial

Address_____ Age_____ Sex_____
_____ Occupation_____

Phone _____ Birthplace_____

Number of years lived in California_____ Race _____

Previous skin cancer_____ _____
yes no

Usual physican
and address _____
_____

Presumptive diagnoses (check and locate on anatomical diagram)

1. Actinic keratosis
2. Basal cell carcinoma
3. Squamous cell carcinoma
4. Leukoplakia
5. Bowen's Disease
6. Melanoma
7. Normal skin
8. Other (specify)

Degree of actinic damage:

mild
moderate
severe

Examiner_____

Physician notified of abnormal skin findings by American Cancer Society on

_____(date)

American Cancer Society Booth
Stanislaus County Fair
Turlock, California August 6-11, 1973

Figure 1.—Registration form used in skin cancer screening booth.

partment working on different evenings. A tiny examining room was formed with portable screens surrounding a single chair, goose-necked lamp and small cabinet. Only sun-exposed skin areas (face, neck, upper chest, arms and hands) were examined in most cases, so that it was not necessary for clothing to be removed. Other skin areas were examined upon request. The average examination took two to three minutes, with less time for children and longer times for complicated problems.

TABLE 1.—*Checklist Used in Making Presumptive Diagnosis*

1. Actinic keratosis	5. Leukoplakia
2. Basal cell carcinoma	6. Bowen's disease
3. Squamous cell carcinoma	7. Normal skin
4. Melanoma	8. Other (specify)

Records were kept on cards filled in both by the physician and by the person being examined (Figure 1). After the visitor supplied personal information, the physician estimated the degree of sun damage (none, mild, moderate, severe) and checked off a presumptive diagnosis from a list of seven common lesions (Table 1). The location of suspicious lesions was noted on an anatomical sticker pasted to the card. Later, the presumptive diagnosis and the location of the lesion were recorded on a postcard that was mailed to the patient's usual physician. The postcard also contained an explanation:

"Your patient _____ was recently screened for skin cancer in the American Cancer Society Booth at the Stanislaus County Fair in Turlock. Abnormal findings were called to the

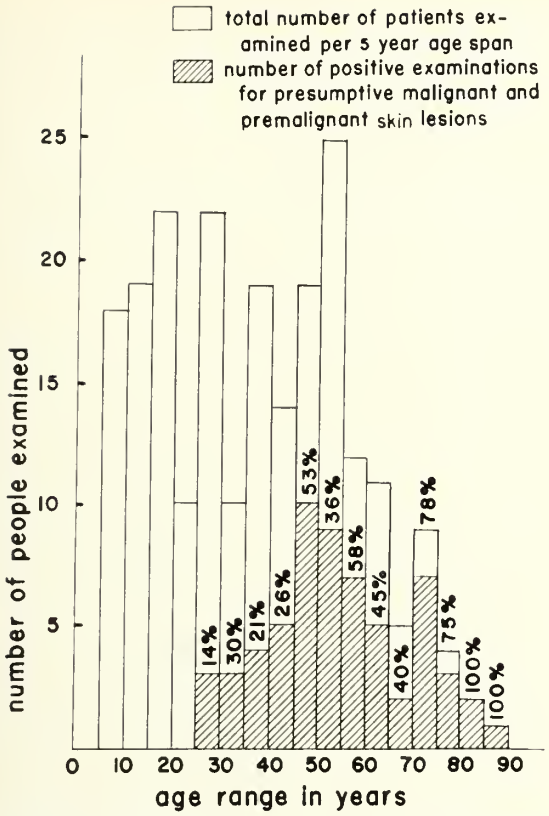

Figure 2.—Distribution by age of normal and abnormal examination results in men.

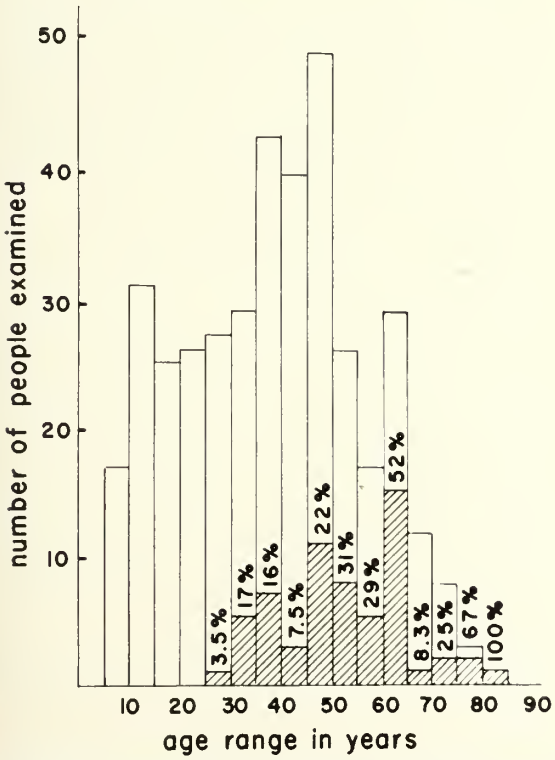

Figure 3.—Distribution by age of normal and abnormal examination results in women.

attention of the patient, who will hopefully contact you for advice in the near future. Additional information is available in our Modesto office."

Results

Community response to the booth was generally favorable, with most visitors expressing appreciation for the time and effort given by volunteers. Many people sought advice for specific skin problems, while others came because of curiosity or a desire to please a concerned spouse. A few people questioned the program's legitimacy and motives. Several also requested that records not be sent to their physicians, apparently from fear of offending them. A few physicians in the area opposed the booth on the principle that it represented "curbstone" medicine.

Skin examinations were done on 605 people, including 222 men and 383 women, ranging in age from 3 to 89 years old. Distribution of normal and abnormal results of the examinations by sex and age group is shown in Figures 2 and 3. While 370 people had normal skin and 85 more had only minor skin problems, 149 had significant skin problems deserving medical attention. Of these 149 people, 135 were eventually referred for treatment to their personal physicians. In 14 cases, information was too incomplete to enable referral.

Presumptive diagnosis of malignant and premalignant skin lesions was made in 125 people, including 63 men and 62 women, ranging in age from 25 to 89 years. Suspicious lesions included basal cell carcinoma in 49, squamous cell carcinoma or possible Bowen's disease in 11, leukoplakia in 8 and actinic keratosis in 88 people. Table 2 shows the exact distribution of lesions by sex. Most lesions were on sun-exposed areas, although one basal cell carcinoma and two squamous cell carcinomas were seen on legs. Leukoplakia was detected only on lower lips, as complete oral examinations were not attempted. Two types of potential skin cancer were present in 31 people, with actinic keratoses occurring together with

TABLE 2.—*Presumptive Clinical Diagnosis of Malignant and Premalignant Skin Lesions*

	Male	*Female*	*Total*
Basal cell carcinoma	24	25	49
Squamous cell carcinoma and Bowen's disease	5	6	11
Leukoplakia	7	1	8
Actinic keratoses*	48	40	88

*In 31 people, actinic keratoses occurred along with basal cell carcinoma (19), squamous cell carcinoma (8) and leukoplakia (4).

TABLE 3.—*Significant Nonmalignant Skin Lesions*

Age/Sex		*Presumptive Diagnosis*
6	♀	Dermatophyte infection-cheek
15	♀	Atopic hand eczema
19	♀	Irritated nevi on back
19	♀	Acne and tinea versicolor
20	♀	Tinea versicolor
20	♀	Nickel allergy and "mole"on labia (not examined)
23	♀	Irritated nevi on back
24	♀	Chloasma
26	♀	Seborrheic dermatitis-postauricular
30	♀	Bleeding nevus
43	♀	Syringomas
46	♀	Lichen simplex chronicus-forearm
47	♀	Xanthelasma
59	♀	Xanthelasma
59	♀	Red nodule-tongue
61	♀	Giant skin tag vs. neurofibroma
62	♀	Blue nevus-forehead
62	♂	Stasis dermatitis
64	♀	Xanthelasma
69	♀	Flesh-colored papule-cheek
71	♀	Violaceous nodules-forearm
75	♀	Hutchinson's freckle vs. senile lentigo

basal cell carcinoma, squamous cell carcinoma or leukoplakia. The youngest age at which each type of lesion was detected was 25 for basal cell carcinoma, 28 for actinic keratosis, 39 for squamous cell carcinoma and 40 years old for leukoplakia. Grouping of lesions into five-year age groups showed peaks at age 45 to 50 for men and age 60 to 65 for women (Figures 2 and 3). No malignant or premalignant lesions were seen in people younger than 25 years of age. No melanomas were detected.

Significant nonmalignant skin lesions were found in 22 people (Table 3) who therefore were referred for treatment. These included 21 women. Nine lesions were felt to warrant skin biopsy to enable exact identification.

Discussion

Previous skin cancer detection clinics in Virginia and North Carolina had overall detection rates of 21.6 percent and 37.8 percent respectively.[2,3] In this study the overall detection rate for potential skin cancer was 20.6 percent. If significant nonmalignant skin lesions were included, the detection rate increased to 24.3 percent. Therefore, almost one out of four skin examinations produced a significant finding. For people 25 years of age and older, the effective cancer detection rate was 28.6 percent, or 125 out of 438 examinations.

Since no potentially malignant skin lesions were found under age 25, exclusion of the younger age group would seemingly save time and be medically safe except for melanoma detection. However, this might greatly hamper instruction of young persons about the hazards of sunlight and the value of protective clothing and sunscreens. Such advice is particularly important for Causasions with red or blonde hair, blue eyes and fair complexions—who form the group most at risk for developing skin cancer.[4]

No attempt was made in this study to verify presumptive diagnoses or trace individual follow-up treatment. While such measures are necessary to assure proper care and firm statistics, they require a great deal of volunteer time, perseverance and effort. It was hoped in this project that individual patients would take responsibility for seeking medical care and that physicians in the area would willingly examine and treat skin lesions called to their attention.

Future skin cancer screening programs should probably limit examinations to people 25 years old or older, except for evaluation of specific skin problems such as changing "moles" in younger persons. Education about skin cancer and its relationship to prolonged sun exposure could perhaps be carried out in an adjacent area by a physician not involved in making examinations. Distribution of free sunscreen samples, as done at the North Carolina State Fair, would probably help draw visitors to the booth. Detection of oral cancer could easily be added to such a program, providing that sufficient space were available to accommodate a dental examination chair and proper light source.

The benefits of such screening programs should be substantial, with early detection of skin cancer leading to prolongation of life and reduction of future required medical care. Possibly, the greatest long-term benefit could be cancer prevention through mass education concerning the hazards of prolonged sun exposure and the usefulness of sunscreens. Additional benefits to participating volunteers include the personal satisfaction of useful community service and the enjoyment of friendly interaction with local residents in a relaxed environment.

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Introduced Schistosomiasis

Evaluation as a Public Health Hazard

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Schistosomiasis was found in many agricultural workers from Yemen who are residing in the San Joaquin Valley, and a study was done to evaluate the public health hazard of this imported disease. If the necessary intermediate hosts are present, a local focus of infection could be established.

Numerous Biomphalaria obstructa snails collected in the vicinity of the Avenue 82 irrigation canal near Oasis, Riverside County, showed no evidence of natural schistosome infection. Laboratory-reared offspring of these snails were exposed to miracidia of Schistosoma mansoni originating from Yemen immigrants and to miracidia from a standard laboratory strain of Puerto Rican origin obtained from the National Institutes of Health. All exposures of California B. obstructa were made with a laboratory stock of highly susceptible B. glabrata snails also obtained from NIH as controls. Although miracidia penetrated California snails no evidence of infection was detected whereas the B. glabrata controls showed normal, mature infections with numerous cercariae.

There appears little likelihood that B. obstructa can serve as intermediate host for schistosomiasis.

THE DISCOVERY OF A LARGE NUMBER of persons in California infected with schistosomiasis has raised the question of possible establishment of this disease within the state. The infected population consists of agricultural workers originating from Yemen and now resident mainly in the San Joaquin Valley. Their number has been estimated at about 2,000, about half of whom show evidence of infection.[1] The present study was undertaken to evaluate the hazard of this imported disease to the general population.

Schistosomiasis is caused by trematode worms which inhabit the mesenteric or vesicular veins of man. Eggs produced by the female worms leave the body and if they should fall into fresh water, release a ciliated swimming larva. This organism, a miracidium, must enter a snail of a certain type in which it undergoes necessary developmental processes that result in the release of large numbers of cercariae. These exit from the snail and

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swim in the water until they encounter an appropriate mammal which they enter by penetration of unbroken skin. There they change to adult forms and repeat the cycle. The establishment of this parasite in any region depends therefore upon the presence of (1) a source of schistosome ova, (2) contamination of freshwater by human dejecta, (3) appropriate susceptible snails, and (4) human contact with this water by swimming or wading. In California, conditions 1 and 4 are met, and 2 may be presumed to occur to some extent. The presence of the proper snail hosts may therefore result in the establishment of a local focus of infection. In the Yemeni workers two species of schistosomes are present. One, Schistosoma haematobium, requires a snail host of a group not known to occur in California, but the other, S. mansoni, passes through snails of the genus Biomphalaria which is found in small numbers in the state.

In March 1972 one of us (G.G.) collected numerous specimens of small Biomphalaria snails from the vicinity of the Avenue 82 irrigation drainage canal near Oasis, Riverside County, adjacent to the Salton Sea. The snails were found mainly on surface vegetation, especially dead saltgrass, and mostly in less than 3 cm of water. It is not known if these snails occur in other parts of California. No evidence of natural schistosome infection was found in more than 100 snails brought to the laboratory. Their offspring have formed the population exposed to schistosome miracidia in the laboratory.

Experimental Procedure

Laboratory-raised snails were exposed to miracidia of S. mansoni both individually and in groups (mass exposures). All ages from newly hatched to mature adult snails were employed. Three strains of S. mansoni were tested: a standard laboratory strain of Puerto Rican origin obtained from the National Institutes of Health, Bethesda, Maryland; a strain from Yemen, isolated in our laboratory from an adult male agricultural worker who was admitted to hospital in Santa Cruz for scrofula; and a strain from the region of Aden, southern Yemen, isolated by us from an adult male immigrant, resident in San Jose. The parasites were maintained in mice and hamsters and in a laboratory stock of a highly susceptible snail, Biomphalaria glabrata, albino stock PR-B, derived from NIH. All exposures of California Biomphalaria snails were made with B. glabrata as controls. Exposed snails were checked at intervals and those not found shedding cercariae after four to six weeks were dissected and examined for signs of schistosome infection.

TABLE 1.—*Infection of Biomphalaria Snails with Schistosoma mansoni, 1972-1974*

Strain of S. mansoni	*B. glabarata**	*B. obstructa*
*Puerto Rico**		
Number exposed	..	165
Number surviving	..	110
Number infected	>80%	0
Southern Yemen		
Number exposed	121	162
Number surviving	85	90
Number infected	39	0
Yemen†		
Number exposed	18	10
Number surviving	17	9
Number infected	7	0

*Our routine laboratory combination in use for several years; thousands of snails have been infected.

†This strain did not grow well in mice and was lost on the second passage.

Results

Table 1 shows the number of snails exposed to each strain of S. mansoni, and the results. Although miracidia were seen to penetrate into the California snails, cercariae were never shed and no evidence of infection was detected upon dissection. The B. glabrata controls had normal, mature infections with numerous cercariae.

Discussion

The snails collected near Oasis have been identified by one of us (P.F.B.) as Biomphalaria obstructa (Morelet) (Figure 1), known from the southern United States, Mexico, Puerto Rico and Cuba.[2] Previous collections of snails of this type have been made from the Salton Sea area, as in the present case, from the vicinity of tropical fish farms. The classification and nomenclature of these small planorbid snails is chaotic and unsettled; therefore it is difficult to trace records concerning their susceptibility to schistosome infection. However, it seems unlikely that other California planorbid snails could serve as intermediate hosts. About 30 years ago Cram and coworkers[3,4] found similar small snails from Baton Rouge, Louisiana, susceptible to a strain of Puerto Rican S. mansoni, achieving a 9 percent infection rate in their exposures. Subsequent studies by McQuay[5,6] confirmed susceptibility in the Baton Rouge population but found New Orleans snails

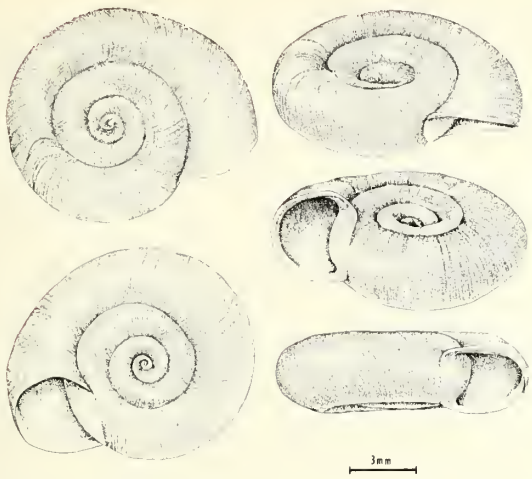

Figure 1.—The shell of Biomphalaria obstructa. (Reproduced by permission from Pan American Health Organization, Scientific Publication No. 168.)

of the same species entirely refractory. Many collections of similar snails from various states all yielded negative results with S. mansoni.[7] The Louisiana snails were identified as Tropicorbis havanensis, which is the same species complex as B. obstructa[8] and is closely related to or perhaps identical with the California form. In south Florida, drainage canals teem with small snails tentatively identified by Leigh[9] as B. obstructa. The presence of many infected Puerto Rican farm workers in that area suggested a study similar to the one reported here, and no infections could be induced in the Florida snails.

We do not know whether B. obstructa is native to California or introduced, perhaps with exotic fish or aquarium plants. Its present known distribution is limited and although it may extend its range in the state there appears little likelihood that it can serve as an intermediate host for schistosomiasis.

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Medical
PROGRESS

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Recent Advances in the Immunopathogenesis of Systemic Lupus Erythematosus

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Systemic lupus erythematosus (SLE) is a chronic multisystem inflammatory disease having definite etiologic associations with ethnic, genetic, viral and immunologic factors. Its pathologic hallmark, vasculitis, is currently felt to be the end result of an immune-complex mechanism. Several clinical and serologic variants of SLE are recognized including discoid lupus erythematosus (DLE), mixed connective tissue disease (MCTD) and drug-induced equivalents —such as procainamide-induced lupus (PIL). The distinguishing features of these variants as well as their prognosis and therapy are discussed in relation to recent developments in the immunopathogenesis of SLE.

SYSTEMIC LUPUS ERYTHEMATOSUS (SLE) is an immunologically mediated disease characterized by multisystem involvement and a capricious tendency to undergo remissions and exacerbations. The increase in prevalence of this disease has been attributed to its earlier recognition and the longer survival of patients.[1] The disease is more frequent in women of childbearing age, occurring five to six times more commonly in females than in males. A recent epidemiological study comparing the incidence, prevalence, and mortality of SLE showed that the risk of this disease was three times greater in black females than in white females.[1] Increased incidence in blacks was not related to unfavorable socioeconomic conditions, but was attributed to a fundamental defect in the immune response.

Since the discovery of the LE cell in bone marrow preparations by Hargraves in 1948, evidence has accumulated implicating immune mechanisms in the renal and vascular lesions of this disease. Despite improved understanding of this entity, confusion persists concerning the clinical and serologic discrimination of several lupus variants. This review deals with recent developments relating to the immunopathogenesis of SLE and considers clinical and serologic variations among the lupus variants as well as developments relating to their treatment.

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Etiologic Factors

Extensive genetic, viral, serologic and histopathologic investigations have suggested a multifactorial cause contributing to the immunologic abnormalities in SLE.

Genetic Aspects

A definite familial occurrence of SLE has been observed.[2,3] Increased gammaglobulin, antinuclear antibodies and other immunological aberrations have been observed in first degree relatives of patients with SLE.[1-4] Studies of the possible relationship between specific histocompatibility antigens and SLE have produced diverse findings. A variety of HL-A antigens* (A5, A7, A8, A13, W5, W15 and an X type) have been observed in association with an increased risk of developing the disease.[5-11] Whether these observations are merely artifacts attributable to chance, or indeed related to SLE is unclear. A severe C2 complement deficiency, perhaps inherited, has been associated with an increased incidence of infection and a lupus-like syndrome. This suggests another genetic pathway in the development of SLE.[12,13] C2 deficiency is felt to increase host susceptibility to infection, particularly chronic viral infection. In this setting, immunization against deoxyribonucleic acid (DNA) might occur more rapidly with development of clinical SLE.

Virus Association

The role of viral infection as a potential etiologic factor, as a contributor to soluble immune complex formation and as an immunogen for certain antibodies found in sera of SLE patients has been extensively investigated.[14-29] Cytoplasmic inclusions resembling the nucleocapsid of paramyxovirus have been observed in the skin and kidney of patients with SLE.[14-18] However, attempts to culture viruses from specimens showing intracellular inclusions failed to demonstrate an active agent.[19] It is currently felt that these tubular structures represent a cellular reaction to viral infection rather than the actual nucleocapsid of a virus.[20] These initial observations fostered a series of studies for circulating antibodies against virus strains in sera of SLE subjects. Initially, two paramyxoviruses, measles and parainfluenza-1, were found to have a high association to SLE by virtue of higher serum antibody levels.[21,22] Unlike the nonspecific observations with intracellular tubular structures, other connective tissue disorders do not demonstrate similar levels of increased antibody to these viruses.[23]

Further studies implicate other viruses to SLE (such as respiratory syncytial, herpes virus, rubella, parainfluenza-2 and -3, reovirus-2, Epstein-Barr virus and hepatitis-associated antigen).[24,25] Recently, Rothfield and associates have suggested that chronic Epstein-Barr virus infection, secondary to impaired cellular immunity, may be an important etiological factor in certain patients with SLE.[27] Sensitive radioimmunoassays have demonstrated antibodies to reovirus double stranded ribonucleic acid (ds-RNA) both in patients with SLE and in New Zealand Black and New Zealand White (NZB, NZW) mice.[28,29] There is no significant amount of ds-RNA in normal mammalian cells. Since the only recognized naturally occurring ds-RNA's are the replicative forms of RNA viruses, it is tempting to speculate that such a virus infection may be responsible for the development of these antibodies in patients with SLE.

Genetic-Viral Interactions

The roles of both viral and genetic factors have become well established in both murine and canine lupus.[30-32] In NZB mice, the lupus diathesis depends on a genetically determined hyperreactivity to nuclear antigens, with a superimposed viral infection to activate this responsiveness.[30] Mating experiments with affected dogs suggests the presence of a transmissible agent in first filial generation puppies.[31] In recent experiments, cell free filtrates prepared from spleens of SLE dogs were injected into normal newborn dogs and mice. This resulted in the induction of serologic abnormalities in the injected animals.[32] Canine recipients developed antinuclear antibodies and positive LE cell phenomena. In some murine recipients anti-DNA antibody was also produced. Many of the latter subsequently developed a viral-induced lymphoma. These results suggest that the SLE canine donors possess a virus capable of inducing the serologic abnormalities of SLE in normal dogs and mice, as well as activation of a latent murine leukemia virus.

The close association of genetic and viral influences in murine, canine and human SLE, and the relationship of disease exacerbations to a variety of drugs, trauma, infection or exposure to sunlight, suggest an etiologic parallel to the

*Histocompatibility antigens on the surface of nucleated cells determined by a single major chromosomal locus, the HL-A locus.

current theories of viral oncogenesis in human leukemia.[33]

Immunopathologic Features

A consistent, characteristic feature of SLE is the presence of numerous serologic abnormalities, including a wide variety of antibodies directed against nuclear, cytoplasmic and serum protein antigens.[34] Anti-lymphocyte, anti-thrombocyte, anti-erythrocyte and anti-clotting factor antibodies may result in leukopenia, thrombocytopenia, hemolytic anemia or an overt hemorraghic diathesis, respectively.[35-40]

Deoxyribonucleic Acid

Antibodies to purified native DNA were recognized early in the study of the serology of SLE.[41] An important early distinction made was that there are two major antigens; native or double stranded DNA (ds-DNA) and denatured or single stranded DNA (ss-DNA). Antibodies present in sera of patients with SLE were found to be heterogeneous and directed against a variety of determinants in both double and single stranded DNA.[42-45] The importance of this distinction is that antibody to ss-DNA, though almost universally present in SLE, occurs with a broader spectrum of immunologically mediated disease.[45] Both ds-DNA and ss-DNA have been found to alternate with the presence of their respective circulating antibodies in SLE sera.[43] However, ss-DNA occurs with greater frequency in the highest concentrations in sera of patients with SLE.[46] It has been proposed that ss-DNA may be the immunogen for the circulating DNA:anti-DNA complexes which play a vital role in the pathogenesis of lupus nephritis.

Deoxyribonucleoprotein

A third group of antibodies involving DNA are directed against nucleoprotein and require both DNA and protein moieties for their interaction. The active principle in SLE serum responsible for the development of the LE cell phenomenon appears to be mediated by antibodies to deoxyribonucleoprotein.[47] Recent studies employing sensitive primary binding techniques demonstrated that the majority of sera from SLE patients contained antibodies to both soluble nucleoprotein and native DNA and that increased levels of antinucleoprotein antibody paralleled renal disease activity.[48] The source of DNA in the serum of SLE patients remains unknown, although a viral or bacterial origin cannot be entirely excluded. The large concentrations, particularly of ss-DNA, suggest an endogenous origin.

Ribosomes and Ribonucleic Acid

Antibodies to cytoplasmic antigens have also been described. Antibodies to ribosomes occur in a small proportion of SLE patients who usually have severe renal disease.[49] An interesting development in the serology of SLE was the discovery of antibodies to ds-RNA, as well as to RNA-DNA hybrids.[50,51] Interest in these antibodies goes beyond their diagnostic specificity and extends into their possible etiologic relationship to SLE. Antibodies against ds-RNA have been observed during peaks of disease activity, but are also present during clinically inactive periods with no relationship to clinical activity.[52]

Precipitating Antibodies

Agar diffusion techniques have permitted investigators to identify four additional antigenic specificities against which SLE sera often contain antibodies.[53] Antibodies to a soluble, nuclear, nonnucleic acid called Sm protein are confined almost exclusively to SLE sera and occur in 30 to 40 percent of cases.[54] Antibodies to another soluble moiety, similar to Sm but cytoplasmic in origin and called Ro, are seen in 30 percent of SLE sera, but rarely together with anti-Sm antibodies.[55] A small proportion of SLE patients with anti-Ro have been noted not to have antinuclear antibodies. Two additional nuclear and cytoplasmic RNA-protein antigens, Mo and La, have been described.[56-57] The nuclear RNA-protein antigen called Mo is probably related to the RNAse susceptible portion of extractable nuclear antigen (ENA) isolated by Sharp and associates.[58,59] ENA probably represents a composite of the Mo and Sm antigens. Assays using the ENA antigen moiety therefore measure anti-Mo or anti-Sm antibodies in the serum.[34] There appears to be a negative association between anti-Mo and anti-DNA antibodies in SLE sera.

Bovine Serum Proteins

Other antigen-antibody systems have been noted in the sera of SLE patients, therefore supporting the speculation that this syndrome may be the end result of several different immune complex mechanisms. The possibility that ingested antigens are playing some role in the pathogenesis of

SLE received support by the observation of increased antibody activity directed against bovine gammaglobulin (BGG) and albumin (BSA).[60] This hypothesis was strengthened by the presence of a BGG-like material in several SLE sera, and in one case, the coexistence of this material and anti-BGG.[60] A high incidence of anti-bovine immunoglobulin M (IgM) also has been found in the sera of immunoglobulin A (IgA) deficient patients.[61] Serum IgA deficiency has been reported with greater than normal frequency in SLE patients.[62] It is possible that loss of secretory IgA, or other gastrointestinal protective mechanisms, permits a greater concentration of antigenically intact molecules to enter the circulation of these genetically predisposed persons. Recently, a patient was described in whom LE cells, tart cells, antibody to ENA, and reduced serum C3 developed on oral milk challenge.[63] The patient's serum also contained milk-precipitating antibodies.

Cryoproteins

Sera of many SLE patients contains immunoglobulins which precipitate in the cold. These cryoproteins consist of complexes of IgM, immunoglobulin G (IgG) and complement components. They occur during the acute or active phases of the disease and are associated with low levels of serum complement.[64] Whether they play an active role in the pathogenesis of lupus nephritis has not been resolved. An antibody-like material directed toward a thermolabile serum macroprotein, distinguishable from C1q, was recently described in SLE sera.[65] It is associated with disease activity and may represent another system involved in the pathogenesis of SLE.

Immune Complexes

Serological studies therefore suggest the presence of a variety of immune complexes in sera of SLE patients. These immune complexes play a major role in the induction of vasculitis, the pathologic hallmark of SLE.

Kidney

The presence of gammaglobulin, complement and fibrinogen in the glomerular lesions of patients with SLE has been shown by immunohistological techniques.[66,67] Three major patterns of immunoglobulin and complement deposition are generally appreciated (linear, mesangial and granular).[68] Linear deposits of IgG without concurrent localization of complement have been observed in a small proportion of patients. Mesangial deposits are usually found in a characteristic pattern of irregular, homogeneous strands of protein lying between capillary loops. The linear or mesangial patterns are usually not associated with clinical or histological evidence of renal disease. Granular deposits are of two types. In most cases, they are irregular in size and distribution throughout the glomerulus. In a few patients with membranous glomerulonephritis, a fine homogeneous granular deposition may be observed.

The direct participation of circulating immune complexes in the induction of nephritis is supported by the fact that gammaglobulin eluted from involved glomeruli contains a higher proportion of antinuclear and anti-DNA activity than does circulating gammaglobulin.[69] Further proof was provided by the detection of DNA and anti-DNA in the glomerular deposits[69] as well as in the circulation,[43] and by the association of active renal disease with the presence of circulating DNA:anti-DNA complexes and hypocomplementemia.[70,71]

Studies employing semiquantitative electron microscopic and immunohistologic methods demonstrated a relationship between increasing amounts of subendothelial and mesangial deposits.[72] Subendothelial deposits were found only in active renal disease, and were extensive only in the presence of large mesangial deposits. There was an unexpected inverse relationship between the extent of subendothelial and subepithelial deposits. The former were found only with the most active histologic changes, carried a poor prognosis and tended to disappear with time and treatment. On the other hand, subepithelial and intramembranous deposits were not necessarily related to active renal disease, carried an excellent prognosis and tended to persist for long periods of time unrelated to treatment. This appears to substantiate the observations that in almost all SLE patients there is glomerular pathology whether or not clinical nephritis is apparent.[73,74]

Skin

Antibodies, usually of an IgG type, may be found in the skin lesions of as many as 90 percent of patients with SLE and in clinically normal skin of 60 percent of such patients.[75] These antibodies appear in a coarse granular pattern at the dermal-epidermal junction and are felt to represent immune complex deposition similar to that observed in glomerular basement membranes

(GBM). Studies of the acid eluates from both glomeruli and normal-appearing skin of three patients with SLE showed that these eluates contained antinuclear antibodies.[76] These antinuclear antibodies demonstrated anti-DNA or anti-ENA specificity, fixed complement, and were deposited in skin in proportion to the total serum IgG concentration. In two of the three cases, a basement membrane antibody was observed that fixed complement and gave a linear fluorescent pattern. These observations have important pathogenic and clinical implications. Both skin[76] and GBM[68,76] are affected by an immune complex, as well as a separate anti-basement membrane antibody mechanism. Furthermore, careful studies of normal and involved skin in SLE patients may reflect to a large extent what is present in the kidney and may obviate the risks of renal biopsy.[77,78]

Central Nervous System

Central nervous system (CNS) disease in lupus appears to be associated with vasculitis involving small blood vessels.[79] Necrosis, thrombi and proliferative changes in arterioles and capillaries have been found to occur with microinfarcts. Considerable evidence exists to support the contention that CNS lupus is also mediated by soluble immune complexes associated with activated components of the complement system.[71,80-86]

Complement

Total hemolytic complement levels are depressed at some time in most patients with systemic lupus erythematosus, while levels are generally normal in patients with discoid lupus.[87] Analysis of complement components in sera from patients with active SLE has demonstrated low levels of C1q, C1s, C4, C2 and C3, although C5 levels were reported as normal.[88,89] These low levels of complement are presumed to reflect complement fixation by immune complexes forming in the circulation and being deposited in certain tissues. SLE sera with low complement levels has been found to be anti-complementary secondary to a high molecular weight fraction containing gammaglobulin, presumably either as aggregates of gammaglobulin or of immune complexes. Highly purified C1q, which readily precipitates in gel diffusion with immune complexes or aggregates of gammaglobulin, has been shown to precipitate with hypocomplementemic lupus sera.[90]

Recent studies have provided evidence to implicate the alternate pathway of the complement system in the pathogenesis of some cases of SLE.[91,92] C3 proactivator is notably decreased in active lupus. There is an excellent correlation between serum C3 and C3 proactivator. Serum properdin levels are also decreased in active disease, and may be participating in the development of lupus nephritis. It is of interest that 20 percent of a group of patients with SLE were found to have properdin deposited along the skin basement membrane associated with C1q, C4, C3, C5 and immunoglobulins.[93] C3 proactivator was observed in the skin of fewer persons.

Cell-Mediated Immunity

Developments in humorally-mediated events of SLE have been presented to substantiate their apparent major role in mediating tissue damage. However, some exciting developments have evolved to implicate an alteration in cellular immune mechanisms in the mediation of this disease syndrome. A variety of studies have indicated that lymphocytotoxic antibody activity is present in the sera of patients with SLE.[35,36,94] These antibodies appear to have T-cell, and possibly HL-A, specificity.[36] A relative and absolute decrease in T-lymphocytes and cells bearing a receptor for C3 has been reported in active lupus.[94] The absolute number of cells bearing surface immunoglobulin was slightly reduced, whereas the proportion of these cells was increased. There is sufficient evidence to postulate that the increased numbers of autoantibodies and the depressed delayed hypersensitivity seen in SLE is due to a decrease in T-lymphocyte function. This hypothesis is supported by a study comparing humoral and cellular immune reactivity to DNA in patients with SLE.[95]

Immunopathologic Summary

A schematic presentation of a possible sequence of steps leading to the induction of SLE is shown in Figure 1. It is believed that a variety of genetic factors predispose persons to the future development of this condition. Superimposed on this genetic endowment, the development of chronic viral infection appears to be an equally important participant in its pathogenesis. The interaction between cell-incorporated viral DNA and a variety of potential subsequent infectious agents, chemical trauma or physical trauma may result in destruc-

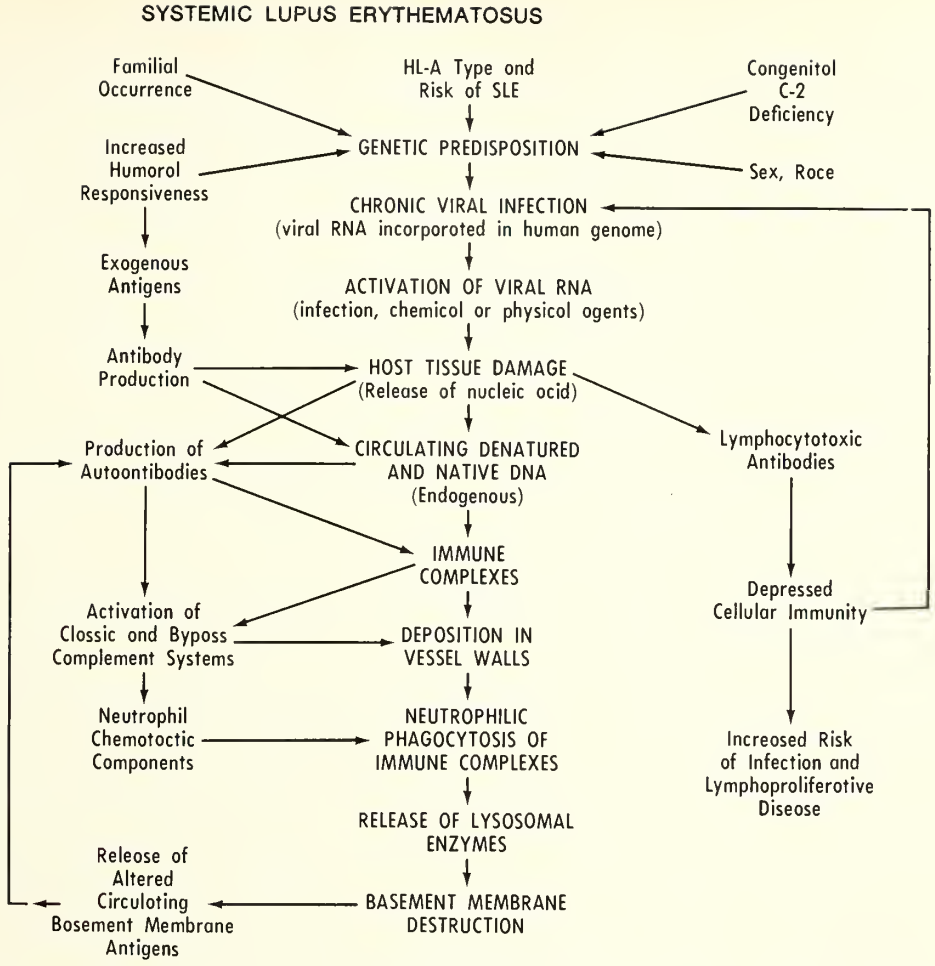

Figure 1.—A schematic presentation of a hypothetical sequence of events leading to the induction of systemic lupus erythematosus.

tion of host tissue with release of nucleic acid materials, in particular ss-DNA, into the circulation. The congenital tendency to increased humoral responsiveness results in the production of a spectrum of autoantibodies against both nucleic and cytoplasmic antigens with the subsequent formation of circulating immune complexes. Exogenous nucleic acids and other foreign substances may also contribute to this humoral response. Circulating immune complexes activate the complement cascade system with the generation of neutrophilic chemotactic components. The immune complexes and activated components of the complement system are deposited on vascular endothelium. The influx of phagocytic polymorphonuclear cells undergoes destruction by terminal components of complement, with release of lysosomal enzymes which inflict damage on the endothelium. Release into the circulation of altered basement membrane antigens may then act as a self-perpetuating system to induce cytotoxic antibodies which may further interact with basement membrane. Autoantibodies directed against T-lymphocytes inhibit cell-mediated immunity, and accentuate the vulnerability of these patients to a variety of viral infections and the earlier development of malignancy.

Clinical Variants

In the last decade, major advances in the immunopathogenesis of SLE have stimulated a reappraisal of the relationship among SLE, discoid lupus erythematosus (DLE) and drug-induced equivalents of SLE—such as procainamide-induced lupus (PIL). Moreover, recent observations by Sharp and associates suggest the existence of an apparently distinct syndrome, referred to as mixed connective tissue disease (MCTD) sharing many clinical features of SLE.[58,59,96,97] Whether this condition represents a separate entity or a milder form of SLE is somewhat controversial at this time.[34,98] Nevertheless, there appears to be little question that the clinical course of these four major variants differs notably. Their discrimination therefore becomes clinically important on prognostic and therapeutic grounds. The clinical and serologic features of these lupus-like syndromes are briefly described here and a summary

TABLE 1.—*Incidence of Specific Clinical Features in Four Major Lupus Syndromes—Systemic Lupus Erythematosus (SLE), Discoid Lupus Erythematosus (DLE), Mixed Connective Tissue Disease (MCTD) and Procainamide-Induced Lupus (PIL).*

Clinical Measurements	*SLE (Percent)*	*DLE (Percent)*	*MCTD (Percent)*	*PIL (Percent)*
Arthritis arthralgias	77-92	38	96	91
Fever	84-100	6	32	39
Pleuritis	24-57	8	25*	52
Pericarditis	15-45	2		18
Raynaud's phenomenon	6-19	9	84	5
Swollen hands	Rare	0	88	0
Dysphagia	Rare	0	77	0
Myalgia	48	Rare	96	27
Myositis	Rare	0	72	0
Malar rash	40-57	100	15	13
Central nervous system symptoms	26-44	3	0	26
Lymphadenopathy	37-68	0	68	9
Splenomegaly	9-41	2	21	5
Hepatomegaly	23-44	0	28	11

References: SLE 99-103; DLE 123-125; MCTD 59, 96, 97; PIL 103, 141, 150, 153.

*Percent having polyserositis.

TABLE 2.—*Incidence of Specific Serologic Abnormalities in Four Major Lupus Syndromes—Systemic Lupus Erythematosus (SLE), Discoid Lupus Erythematosus (DLE), Mixed Connective Tissue Disease (MCTD) and Procainamide-Induced Lupus (PIL)*

Laboratory Measurements	*SLE (Percent)*	*DLE (Percent)*	*MCTD (Percent)*	*PIL (Percent)*
Anemia	57-75	Rare	48	21
Leukopenia	43-65	28	52	33
Thrombocytopenia	5-7	5	8	4
Elevated ESR	84	47	80	60
Biological false-positive VDRL	22	6	0	0
Antinuclear antibodies*	>95R,D,S	30D	>95S,R	>95D
Positive lupus erythematosus cell	76-100	5	20	94
Antibody to ENA	55	0	100	?
Antibody to Sm antigen	30-40	?	0	?
Antibody to ds-DNA	83-100	14-86	12	0
Antibody to ss-DNA	85-100	50-80	16	50
Antibody to ds-RNA	70	42	?	12
Hypocomplementemia	90-100	0	0	0
Celluria/proteinuria	46-70	0	0	0
Abnormal kidney biopsy	95-100	?	?	?
Abnormal skin biopsy†	90/60	95/0	?	90/<5

References: SLE 34, 43, 48, 50, 58, 59, 72-74, 78, 89, 103, 105-114; DLE 123-128; MCTD 34, 59, 96, 97, 107; PIL 130, 141, 150, 153.

*R = rim; D = diffuse; S = speckled.

†Expressed as percent with positive band fluorescence in abnormal skin/percent with positive band fluorescence in uninvolved skin.

of their clinical serologic similarities and differences is presented in Tables 1 and 2.

Systemic Lupus Erythematosus

A great spectrum of symptoms and signs, single or in combination, are currently considered as possible clinical expressions of SLE (Table 1). Although the symptoms reflected in acute, active SLE have changed little from classic earlier descriptions,[99-103] we are currently able to diagnose the disease at a much earlier stage, when it manifests less dramatic signs. We have come to appreciate that this disease is frequently insidious in its onset. Vague constitutional symptoms including low grade fever, weakness, easy fatiguability and weight loss may be the only symptoms. Certain organ systems have a great predilection to become involved in the course of the disease.

The skin, musculoskeletal system and serosal membranes are frequently affected sites. The most common cutaneous feature of SLE is an erythematous rash, often symmetrical, over the face and exposed surfaces of the body. Frequently, the patient reports a diffuse increase in hair loss, and occasionally a history of frank patchy alopecia is elicited. Other skin manifestations may include a characteristic periungual erythema, nonspecific ulcerations of the mucous membranes, erythema nodosum, urticaria and angioedema.

Polyarthralgia or arthritis is typically asymmetric and migratory and may be associated with severe myalgia. Infrequently the arthritis may be severe, symmetric and associated with deformity indistinguishable from rheumatoid arthritis. Very rarely the arthritis may be associated with subcutaneous nodules resembling rheumatoid granulomas. However, the arthritis of SLE is usually very transient and rapidly responds to therapy.

Polyserositis is also common and may take the form of a pleuritis or pleuropericarditis with or without effusion or an underlying pneumonitis. Proliferation of lymphoid tissue may manifest itself in a prominent lymphadenopathy. Splenomegaly and hepatomegaly may also be observed in the active case. Emotional lability, frank psychoses, convulsions, cranial nerve palsies and peripheral neuropathy suggest active CNS lupus. The appearance of peripheral edema coupled with hypertension and an abnormal urinary sediment indicates nephrosis which is observed in 25 percent of patients. In fact, overt nephritis appears to be quite characteristic of SLE, occurring in 60 percent of patients. This distinguishes SLE from DLE, drug-induced variants and mixed connective tissue

disease where overt renal disease generally does not occur.

The incidence of serologic and other laboratory aberrations of classic SLE are summarized in Table 2. Detection of antibodies to a variety of nucleic and cytoplasmic antigens will vary considerably with the diverse techniques employed to measure them.[52,104] Their presence is also dependent on disease activity and whether or not the patient has been actively treated. Since there are no reports quantitating all measurements simultaneously in the same population of untreated patients, the incidence of serologic aberrations summarized in Table 2 should be interpreted as a rough approximation. Several serologic features appear to be extremely useful in delineating patients with classic SLE. Antinuclear antibodies should be detected universally in the serum from untreated lupus patients with active disease if searched for by an indirect fluorescent antibody technique. The patterns of nuclear staining most commonly seen are (1) the rim or shaggy pattern associated with antibodies to either DNA or nucleoprotein, (2) the diffuse pattern associated with antibody to nucleoprotein and (3) occasionally the speckled pattern associated with antibody to Sm antigen or ribonucleoprotein.[58,105-107] Though its sensitivity makes it a useful screening test, a positive result in no way establishes the diagnosis of SLE. The LE cell test is somewhat more difficult to do and is highly dependent on the observer's judgment and skill. Though a positive LE test can occasionally be seen in rheumatoid arthritis, systemic sclerosis and chronic active hepatitis, it carries a greater degree of specificity for SLE. The chances of obtaining a positive initial test in untreated SLE varies between 30 percent and 60 percent. However, over the course of an illness, sequential tests would yield a positive result in nearly every patient.[108] Antibody to ds-DNA associated with hypocomplementemia shows the greatest degree of specificity for SLE.[89,109-113] Recently, it has been demonstrated that the presence of circulating DNA:anti-DNA complexes nearly always represents active disease and persistence of these complexes carries the implication of a poor prognosis.[70,71]

The early evaluation of SLE patients by percutaneous renal biopsy has indicated that few, if any, are free of detectable abnormalities when studied with fluorescent and electron microscopy in addition to light microscopy.[68,73,74] Although virtually nothing is currently known of the histologic status of the kidney in patients with DLE, MCTD or drug-induced equivalents, the absence of urinary sediment or biochemical abnormalities in these patients is in stark contrast to observations in patients with classic SLE. Excluding specific medical contraindications, percutaneous renal biopsy offers an excellent method of establishing the extent of major organ involvement, as well as a definite clue to prognosis.[72,73] Preliminary data suggest that fluorescent studies of skin tissue may mirror, to a large extent, findings in the kidney and may eliminate the risks of renal biopsy in the future.[77] Direct fluorescent antibody studies on clinically normal skin from patients with suspected SLE may be an invaluable tool in establishing the diagnosis. Where 60 percent of normal skin biopsies will be positive for immunoglobulins at the dermal-epidermal junction in SLE, patients with DLE or drug-induced equivalents are invariably negative.[78,114]

A recent report suggested that SLE patients who survived the first five years of disease, experienced greater morbidity and mortality as a result of CNS lupus.[73] Our personal experience certainly supports this observation. Considerable evidence has accumulated to support an immunological mediation of CNS lupus.[79,86,115] However, rapid and accurate discrimination of the neuropsychiatric manifestations of lupus from the behavorial effects of corticosteroids or other frequently employed drugs, metabolic aberrations, infection and cerebral thrombosis, poses a considerable diagnostic problem.[79,80,85,116-118] Antibodies to DNA, DNA:anti-DNA complexes, depressed levels of C4 and decreased concentrations of IgG have been noted in the cerebrospinal fluid of patients with CNS lupus.[71,80-82,115] The availability of such techniques should improve our ability to differentiate active CNS lupus from other possible causes of CNS disturbances in SLE.

Since the original publication of preliminary criteria for the classification of SLE under the auspices of the American Rheumatism Association,[119] their reassessment and clinical application have resulted in suggestions for modification.[120-122] Table 3 lists these criteria; if four of the 14 major criteria are positive, there should be a 98 percent specificity for SLE. A recent report supports the usefulness of these criteria when applied to patients with early SLE and rheumatoid arthritis.[122] The sensitivity of these features was found to be 88 percent with specificity against rheumatoid arthritis at 98 percent. Sensitivity could be in-

TABLE 3.—*Preliminary Criteria for Classification of Systemic Lupus Erythematosus*

1. Facial erythema (Butterfly Rash)
2. Discoid lupus
3. Raynaud's phenomenon
4. Alopecia
5. Photosensitivity
6. Oral or nasopharyngeal ulceration
7. Arthritis without deformity. (One or more peripheral joints involved with any of the following in the absence of deformity—(a) pain on motion, (b) tenderness, (c) effusion or periarticular soft tissue swelling)
8. Lupus erythematosus cells
9. Chronic false-positive standard test for syphilis
10. Profuse proteinuria
11. Cellular casts
12. One or both of the following—(a) pleuritis, (b) pericarditis
13. One or both of the following—(a) psychosis, (b) convulsions
14. One or more of the following—(a) hemolytic anemia, (b) leukopenia, (c) thrombocytopenia

creased to 92 percent, without loss of specificity, when increased titer of antinuclear antibodies was employed as an alternative to the LE cell test. These criteria do not require sophisticated serologic tests and should serve as a practical universal guideline for diagnosis.

Discoid Lupus Erythematosus

The relationship between DLE and SLE has intrigued clinicians for years, not only on theoretic grounds, but also for diagnostic reasons. Based on sex incidence (2:1 male to female ratio), clinical symptomatology (Table 1), laboratory findings (Table 2), as well as a more favorable prognosis, the two conditions must be considered separate, though undoubtedly closely related.[123,124] Clinically, DLE is characterized by cutaneous lesions which consist of well-defined red to violaceous papules and plaques with somewhat elevated active borders and scaly, paler centers. As the lesions mature, atrophy and scarring appear in their centers and telangiectasis is occasionally observed in atrophic areas. These lesions can be localized or widespread over various parts of the body. Rothfield and associates compared patients with chronic DLE with matched controls and found that systemic disease was observed in only a small number of the former.[125] Polyarthralgia is a clinical feature in a third of these patients.

More than one-half of DLE patients have some laboratory abnormalities commonly associated with SLE.[126,127] Although anemia and thrombocytopenia are infrequent, leukopenia has been noted in approximately 25 percent of DLE patients. The erythrocyte sedimentation rate is frequently elevated and nearly a third of DLE patients have antinuclear antibodies usually manifesting a diffuse pattern on fluorescent studies. Though it has been stated that DLE patients with antinuclear antibodies run the same risk of developing SLE as those who are seronegative,[126] studies employing sensitive assays for ds-DNA support the predictive value of increased levels of antibody to ds-DNA and subsequent development of SLE.[127] Though patients with DLE may demonstrate increased levels of antibody to ds-DNA, it is never associated with hypocomplementemia. Recent studies have demonstrated circulating antibody to ds-RNA in 42 percent of patients with DLE as compared with 70 percent in SLE.[128] The latter together with the observations of circulating anti-ds-DNA antibody[127] substantiate the fact that DLE is a part of the SLE spectrum. In fact, a small proportion of DLE patients, about 5 percent, go on to develop overt SLE.[123-125]

Of major prognostic and therapeutic importance are the absence of renal and CNS involvement and favorable responses to local steroid therapy or antimalarial compounds or both. Diagnostically, a useful distinguishing feature is the complete absence of immunoglobulin deposition at the dermal-epidermal junction in uninvolved skin when studied by fluorescent microscopy.[78]

Though the issue of its precise relationship to SLE must remain unsettled, considerable agreement exists to support the contention that DLE is to a large degree a cutaneously expressed aberration capable of remaining confined to this organ indefinitely.[124-126] Therapeutic endeavors must be tempered accordingly and discriminating DLE from SLE becomes highly important.

Mixed Connective Tissue Disease

Over the past decade, studies by Sharp and his colleagues led to the description of a group of patients whose clinical syndrome suggested the coexistence of several autoaggressive disorders (SLE, systemic sclerosis and polymyositis). The syndrome was termed mixed connective tissue disease (MCTD).[58,59,96,97] Patients with this syndrome resemble those with SLE as they suffer a high incidence of polyarthralgias and non-deforming arthritis, may have recurrent difficulties with polyserositis and occasionally manifest typical cutaneous lesions (Table 1). Lymphadenopathy and

hepatosplenomegaly are seen to a similar degree as in SLE. MCTD differs clinically from classic SLE due to the high incidence of swollen, sclerodermatous-like hands, dysphagia with abnormal esophageal motility, Raynaud's phenomenon and an active myositis. Cutaneous changes typical of dermatomyositis are occasionally seen over the eyelids and metacarpal-phalangeal joints. CNS symptoms are not a feature of this entity. Prognostically the course is usually mild with characteristically excellent response to corticosteroids.

The serologic findings common to all patients with MCTD are (1) high titers of antinuclear antibody giving a speckled (infrequently, rim) pattern on fluorescent testing, (2) high titers of antibody to ENA with specificity to the nuclear RNA protein, Mo, (3) no detectable antibody to Sm antigen, (4) relative infrequency of antibody to ds-DNA and ss-DNA and (5) normal or elevated levels of serum complement (Table 2). Furthermore, there is a paucity of renal involvement as determined by urinalysis and glomerular filtration rate. It must be pointed out, however, that a systematic study of renal tissue has not been reported. Similarly, fluorescent microscopic studies of skin tissue and their relationship, if any, to other lupus variants is not currently known.

Recently a subgroup of SLE patients, reported by Reichlin and Mattioli, were noted to have serologic features similar to patients with MCTD.[98] Sera from these patients contained antibody to RNA protein and had a low incidence of anti-DNA antibody. Furthermore, there was a paucity of renal disease and their favorable clinical course set them apart from other patients with SLE. This SLE subgroup differed from those with MCTD with respect to the predominant clinical features so frequently seen in the latter. Hence, there is some controversy as to whether the clinical and serologic features ascribed to MCTD warrant the creation of a separate disease entity. It may be more appropriate to distinguish these patients as a specific segment of the obviously heterogeneous SLE community who have immunologic features consistent with a more favorable prognosis. In this respect, it has been suggested that antibody to ENA may exert a protective effect by inhibiting the formation or consequences of DNA:anti-DNA complexes.[59,97] There is some supportive experimental evidence for this hypothesis in the murine lupus model. Weekly injections of ENA were observed to have an inhibiting effect on the induction of renal disease when compared to untreated controls.[129]

TABLE 4.—*Drugs Implicated in the Induction of a Lupus-Like Syndrome*

Procainamide[130,131]	Penicillamine[140]
Hydralazine[132]	Oral contraceptive agents[141,142]
Isoniazid[133]	Phenothiazines[143]
Sulfonamides[134]	Quinidine[144]
Penicillin[135]	Ethosuximide[145]
Tetracycline[136]	Phenylbutazone[146]
Streptomycin[137]	Diphenylhydantoin[147]
p-Aminosalicylic acid[138]	Mephenytoin[148]
Griseofulvin[139]	Trimethadione[149]

Irrespective of whether one agrees with the validity of a separate clinical entity, MCTD or simply a milder form of SLE, it appears certain that some patients with a lupus variant can be discriminated by well-defined serologic and to some degree, clinical, features. These persons rarely manifest either the renal or the CNS complications of SLE, respond briskly to corticosteroid therapy and generally enjoy a more favorable prognosis.

Drug-Induced Lupus

The drugs reported as capable of inducing a lupus-like syndrome, antinuclear antibodies and LE cell test positivity are listed in Table 4. The implication is most convincing for hydralazine and procainamide; and somewhat less so for isoniazid, diphenylhydantoin, mephenytoin and tridione. Most of the other drugs have been reported causing a lupus-like syndrome only sporadically, and their true relationship, in many instances, remains controversial. Pathogenetically, a better understanding of the drug-induced equivalent may be the key to the trigger mechanisms of autoimmunization.

Among the drug-induced syndromes, procainamide and hydralazine appear to initiate different entities and may represent two broad categories of disease. Procainamide triggers a lupus-like syndrome which frequently subsides when the drug is discontinued. Most patients with PIL have no personal or family history of a rheumatic disorder. Hydralazine produces a similar disorder which appears to occur more often in patients with an underlying diathesis. The incidence of a personal or family history of a rheumatic disorder in this group is 74 percent.[150] Its manifestations persist in a higher percentage of patients than with the procainamide-induced form.[150] Patients with active hydralazine lupus develop circulating antibodies to hydralazine, and their lymphocytes undergo blast transformation to hydralazine *in*

vitro.[151] All patients in whom hydralazine lupus develops are slow acetylators of the drug.[152] Patients with hydralazine-induced lupus are similar to those with SLE; sera from these patients contains antibodies to both ds-DNA and ss-DNA. The clinical and other serologic features of hydralazine lupus resemble those of procainamide-induced lupus (PIL) tabulated in Tables 1 and 2.

Currently, procainamide appears to be the most recognized offender in the induction of lupus. Of patients receiving the drug for an appreciable length of time, 75 percent develop antinuclear antibodies, usually with a diffuse pattern of fluorescence.[153] A small percentage of these patients develop a lupus-like reaction characterized by polyarthralgia, myalgia, fever and pleurisy (Table 1).[131,132,150,153] As with DLE, the preponderance of males affected is in striking contrast to that seen in SLE. Renal and CNS disease are notably absent. The latter has been attributed to a lack of complement-fixing antibodies to ds-DNA. Antibodies to ss-DNA are seen in 50 percent of clinically affected cases. Positive LE cell preparations are very common. It has been suggested that as a result of photo-oxidation, procainamide may combine with DNA and various other nuclear macromolecules to render these substances immunogenic.[131]

Cessation of procainamide is followed by abatement of symptoms within a period of two to three weeks. Occasionally, manifestations of lupus may persist for prolonged periods ranging from 5 to 49 months after the medication is stopped.[150] When necessary, corticosteroids may be employed briefly, and almost universally result in prompt clinical improvement.

Course and Treatment of SLE

A recent study emphasizing the relationship of racial factors and mortality indicated that 62.7 percent of blacks and 64.4 percent of whites had survived after five years of disease.[1] Moreover, the data indicated that the most critical years for survival are the first three or four after diagnosis. In one segment of a New York City population, the fatality was 15.5 percent in the first year, about 8 percent annually in the next three years and from 1 to 5 percent each year thereafter. Various racial groups were comparable in respect to therapy and involvement of major organ systems. It was concluded that ethnic differences were not detectable in survival rates despite racial variations in susceptibility to the disease.

The effect of pregnancy on survival was also studied and indicated that the estimated five year survival rate (ranging between 50 and 54 percent) was lowest for nonpregnant women. For those with one pregnancy after diagnosis, the probability of surviving five years was 80 percent. Differences in outcome could not be explained on the frequency of renal or CNS involvement alone, since these were comparable but depended on the severity of disease at the time of conception and the degree of activation of the disease during gestation and the puerperium.[1]

Dubois and his associates recently reviewed the causes of death in 212 patients with SLE with emphasis on 89 patients in whom autopsies had been done.[154] Uremia continued to be the leading cause of death (28 percent) with CNS complications (15 percent), infection (8 percent) and malignancy (4 percent) also playing important roles. As is often the case, multifactorial causes accounted for fatality in 10 percent of cases. The dramatic decrease in CNS complications as well as the significant decrease in uremia as a cause of death was attributed to earlier and more frequent employment of corticosteroids. On the other hand, there was a notable increase in the rate of infections, vascular complications and malignancy in the patient segment studied. It is tempting to ascribe many of these fatal complications to corticosteroids. However, a recent study comparing patients with SLE, rheumatoid arthritis and nephrotic syndrome suggested that the increased infection rate in SLE cannot be attributed to steroid therapy and decreased renal function alone.[155] From what is suspected regarding its fundamental causes (Figure 1), the relationship, if any, between the increased rate of malignancy in patients with SLE and any prior therapy should be interpreted with care. As the rate of survival increases, the rate of malignancy might also be expected to rise on theoretical grounds proportional to the degree of persistent viral infection and depressed cell-mediated immunity.

In that a specific curative agent is not known, the quality and intensity of therapy is highly dependent on the patient's clinical features. Since three of the four variants discussed above are either self-limited or easily controlled with conservative corticosteroid treatment, complete patient evaluation must precede long-term therapeutic decisions.[156-158] General measures including good nutrition and avoidance of sunlight are important considerations in the management of SLE. Salicylates may be effective when the major mani-

festations consist of mild polyarthritis or polyscrositis. In this respect, the clinician should be cognizant of the recent association of aspirin and hepatitis, particularly in patients with SLE.[159] Nonsteroidal anti-inflammatory drugs such as indomethacin may be of benefit when salicylates fail to adequately control musculoskeletal complications.

Once it is determined that an individual patient has acute multisystem SLE, prednisone should be administered in daily doses of 60 mg or more until clinical manifestations have subsided. With satisfactory remission of the disease, the dose of corticosteroids can be slowly and carefully tapered. If control cannot be achieved with dose levels below 15 mg of prednisone daily, the addition of an immunosuppressive drug should be considered.

Diffuse proliferative nephritis characterized by extensive subendothelial deposits, as well as membranous glomerulonephritis, usually requires long-term employment of large doses of steroids before adequate control can be achieved. The myriad of problems attendant with long-term use of corticosteroids and the frequent failure of these renal complications to respond adequately has resulted in the introduction of a variety of immunosuppressive agents as treatment modalities.[156,160-164] Guidelines for the use of such agents have been published.[165,166] Although some controversy still exists,[167,168] there is an impressive body of controlled and uncontrolled data supporting the efficacy of azathioprine and prednisone,[160,163,164,169,170] cyclophosphamide and prednisone,[161,162,170-172] and chlorambucil and prednisone[173] in the treatment of lupus nephritis. Our experience indicates that the best therapeutic responses are achieved by administering low doses of prednisone (10 to 20 mg daily), together with 2 to 2.5 mg per kilogram of azathioprine daily. Upon achieving remission, the prednisone is initially withdrawn slowly. Although a gradual withdrawal of azathioprine is also desirable, many patients may require a minimal dose (such as 50 mg daily) to maintain their disease in a state of remission. The use of these agents appears to reduce, and in some cases, completely avoid the undesirable consequences of long-term treatment with corticosteroids.[169] As with corticosteroids, rapid withdrawal of these immunosuppressive drugs may induce an acceleration of disease, and whenever possible, a gradual reduction is preferred.[169-174]

The value of corticosteroids in the treatment of the neurologic complications of SLE is uncertain. Although dramatic improvement following their use has been observed, there are many patients who fail to respond or worsen during such therapy.[79,80] The psychiatric complications of steroids are frequently difficult to discriminate from the neuropsychiatric manifestations of SLE, frequently posing a therapeutic dilemma which must be resolved clinically for each patient.[175]

There is little doubt as to the vast improvement which has taken place in the prognosis of SLE in recent years. Five-year survivals of nearly 80 percent are currently being reported, even in renal-complicated SLE.[173] This is based not only on an earlier diagnosis, but also on the beneficial effects of corticosteroids and other immunosuppressive agents. The disease no longer poses its formerly serious threat to survival provided that aggressive measures are taken to abrogate serious damage to vital organs. As noted above, early evaluation of renal tissue as well as complement and DNA antibody studies can provide useful information in assessing the course of patients with renal involvement, as well as identifying those who are more likely to develop critical functional impairment.

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Refer to: Inappropriate antidiuretic hormone secretion—Medical Staff Conference, University of California, San Francisco. West J Med 122:145-149, Feb 1975

Inappropriate Antidiuretic Hormone Secretion

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Assistant Professor of Medicine, and H. David Watts, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, CA 94143.

DR. SMITH:* *Our patient this morning presented with an interesting metabolic problem which seems to represent a rare complication of drug therapy. The syndrome of inappropriate secretion of antidiuretic hormone (*STADH*) was first described in 1957 and has subsequently been found in association with a wide variety of disorders. It is an important syndrome to recognize since its treatment is usually simple and effective and also because it may represent the first manifestation of a serious underlying disorder.*

The case summary will be presented by Dr. Michael Jensen, following which the discussion of this problem will be led by Dr. Morris Schambelan from the Endocrine Division of the San Francisco General Hospital.

DR. JENSEN:† The patient is a 74-year-old white woman who was admitted on an emergency basis because of the acute onset of a confusional state. The patient was transferred from another hospital where she had been admitted for one week for evaluation of chronic complaints of indigestion associated with some nausea and vomiting. Upon admission to the hospital, serum electrolyte content was normal. Results of a complete gastrointestinal evaluation, including x-ray studies of the gallbladder and upper gastrointestinal tract and a barium enema, were within normal limits. Administration of amitriptyline was started, 100 mg daily, for depression and it was given for approximately six days. At that time, the patient became confused and lethargic and was transferred to the University of California Medical Center for further care, with no specific diagnosis being apparent.

The history was one of general good health except for chronic degenerative arthritis involving both hands and requiring intermittent indomethacin therapy.

On physical examination, the patient was seen to be very lethargic and somewhat confused. Blood pressure was 175/90 mm of mercury, pulse rate 96 beats per minute and regular, respiratory rate 14 per minute. A general physical examination failed to show any abnormalities but the neurological examination gave abnormal results in that the patient was disoriented as to time and place. There were no focal neurological signs.

On admission, hemoglobin was 14.1 grams per 100 ml, hematocrit 39.4 percent, leukocyte count 12,800 with 83 percent neutrophils, 8 percent lymphocytes and 9 percent eosinophils. Platelet count was 305,000 per cu mm, serum B_{12} level 1,020 pg, sedimentation rate 4 and prothrombin time 10.4 seconds. Electrolytes were decidedly abnormal; serum sodium was 99, potassium 3.6, chloride 66, bicarbonate 25 mEq per liter. Cal-

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cium was 9.1 mg per 100 ml, magnesium 1.8 mg per 100 ml and osmolality 208 mOsm per kg. Phosphorus was 2.3, glucose 103, creatinine .7, uric acid 2.3, blood urea nitrogen (BUN) 13 and total bilirubin 1.0 mg per 100 ml. Total protein 6.8 grams per 100 ml, globulin 2.7 grams per 100 ml, serum glutamic-oxaloacetic transaminase (SGOT) 25 IU per liter, amylase 291 IU per liter, triglycerides 61 mg per 100 ml, cholesterol 229 mg per 100 ml, tetraiodothyronine (T_4) 6.5 μg per 100 ml, T_4 iodine 4.2 mg per 100 ml and triiodothyronine (T_3) 32 percent. Urinalysis gave negative results, with a specific gravity of 1.005. A test of urine for porphyrins gave negative results. Spinal fluid protein was 47 grams per 100 ml, glucose 79 mg per 100 ml. Findings on electroencephalogram, brain scan and skull and chest x-ray studies were normal. A computerized tomographic brain scan showed a calcified pineal that was midline and also the presence of slightly atrophic ventricles. The electrocardiogram was abnormal due to a left anterior hemiblock.

Following admission to the hospital, it became rapidly apparent that the source of impaired consciousness was the severe electrolyte disturbance. The patient was treated with furosemide and isotonic replacement of urine volume and within a matter of three days the serum sodium level was up to 130 mEq per liter with a normalization of the rest of the electrolytes. As the electrolytes became normal, the patient became brighter. A search was made to determine the cause for the apparent inappropriate antidiuretic hormone (ADH) secretion. A complete neurological evaluation was done, as has already been reported.

The chest films did not show any suggestion of a pulmonary neoplasm. Similarly, results of radiographic studies of the gastrointestinal tract were within normal limits.

A very careful drug history revealed that the patient was taking only amitriptyline immediately before the onset of the hyponatremia syndrome. The amitriptyline was discontinued. During the hospital stay, the patient became brighter and oriented. At the time of discharge electrolytes remained normal on a free fluid intake.

DR. SCHAMBELAN:* I would like to begin this morning by reviewing some recent data regarding the normal control mechanisms for the secretion of antidiuretic hormone. With this background, I shall then examine the pathophysiology in this interesting syndrome in which secretion of the hormone is apparently inappropriate for the physiological setting (SIADH). I shall then turn to a consideration of the clinical situations in which SIADH occurs and pay particular attention to drug related causes, apparently the mechanism in the patient presented today.

The antidiuretic hormone in man is an octapeptide arginine vasopressin (AVP). It differs from the other major neurohypophyseal hormone, oxytocin, by virtue of the amino acid residues in the third and eighth positions. In other species, such as hogs, lysine replaces arginine at the eighth position. An intermediate peptide, arginine vasotocin, has been identified in the evolutionary scale and structurally represents a cross between AVP and oxytocin. These peptides are synethesized in the supraoptic and paraventricular nuclei and travel down their axons via the neurohypophyseal tract to the pars nervosa of the posterior pituitary where they are stored and secreted.

The major biological effect of vasopressin appears to be to decrease solute free water clearance by a direct action on the renal tubular epithelium. Hormone secretion is primarily responsive to change in body osmolality and the control mechanism is sufficiently sensitive to maintain osmolality within a 1 to 2 percent range. A precise feedback loop is operative in which a loss of water resulting in an increase in serum tonicity leads to antidiuretic hormone release, presumably mediated by osmoreceptors. Water retention results in dilution and return toward normal tonicity. A parallel mechanism in the hypothalamus involves a thirst center which is also stimulated by the increase in tonicity. Injection of hypertonic saline into the hypothalamus and direct electrical stimulation both result in drinking.

The recent availability of sensitive and specific radioimmunoassays for AVP have confirmed many of the earlier observations that were based on data derived during renal clearance studies or by less sensitive bioassay techniques. Husain et al[1] found low or unmeasurable AVP levels in water loaded subjects and in patients with pituitary diabetes insipidus, whereas, dehydration in normal subjects resulted in variable increases in AVP levels. The relationship between serum tonicity and AVP levels has been recently evaluated by Robertson et al[2] who made simultaneous measurements of plasma osmolality and plasma AVP levels in varying stages of hydration. AVP levels were low in water loaded

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normal subjects but began to increase sharply at approximately 285 mOsm per kg (Figure 1). It was noted that in patients with pituitary diabetes insipidus there occasionally would be measurable levels of AVP but that these were inappropriately low for the state of hyperosmolality. By contrast, elevated levels of AVP were noted in the several patients with nephrogenic diabetes insipidus that he studied.

In addition to an osmotic mechanism, AVP also responds to a variety of nonosmotic stimuli. A number of these such as standing, hemorrhage, application of tourniquets and states associated with a decrease in cardiac output can all be viewed as messages which relate a decrease in effective vascular volume. These stimuli can be so profound as to override osmotic control. This was shown in a recent study by Robertson[2] in which a water loaded normal subject with low or unmeasurable AVP levels had blood pressure lowered acutely with intravenous trimethaphan. Despite maintenance of the plasma osmolality at 280 mOsm per kg or below there was a sharp increase in the levels of AVP.

In addition to osmotic and volume factors, other stimuli for ADH release have been identified. A variety of drugs including nicotine, barbiturates and morphine can directly stimulate AVP release. Some recent studies have shown an increase to levels as high as 200 pg per ml after smoking two cigarettes; these levels are more than 20 times those seen during simple dehydration. A complex neural mechanism is also involved with stimuli such as stress, suckling and coitus resulting in enhanced secretion. Various manipulations of the adrenergic nervous system also exert effects upon the release of AVP.[3]

With this understanding of the physiological control mechanism for ADH one can examine the pathophysiology in SIADH. The first clear definition of such a syndrome was provided by Schwartz and Bartter[4] in their report of two patients with carcinoma of the lung who presented with hyponatremia. In a careful metabolic study they defined a relationship between the hyponatremia and the state of water balance. When fluid intake was increased from 2,000 to 3,000 ml per day the patients gained weight and went into positive fluid balance; sodium excretion increased and hyponatremia developed on the basis of dilution and net sodium loss. This resulted in a hypo-osmolar state and because simultaneously obtained urine osmolality ranged from 280 to 440 mOsm

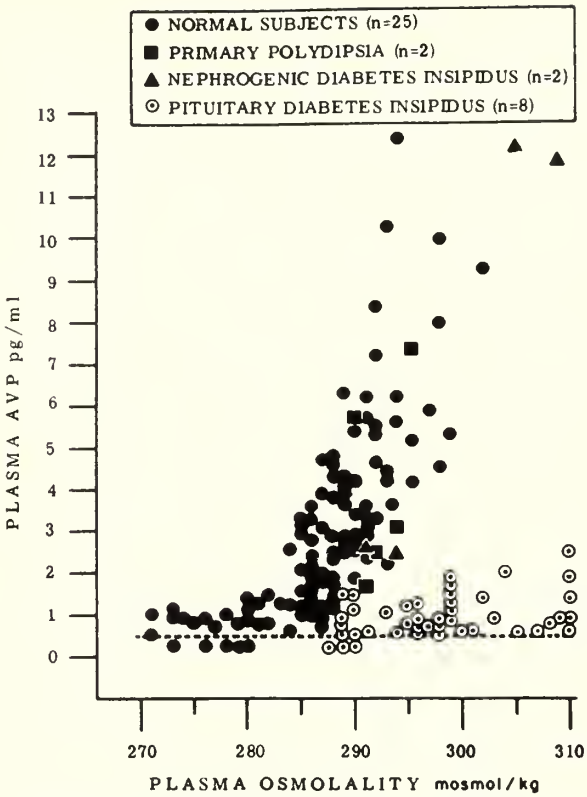

Figure 1.—The relationship of plasma arginine vasopressin (AVP) to plasma osmolality in normal subjects on varying fluid intakes and patients with polyuria of diverse causes. (Reproduced with permission from J Clin Invest[2])

per kg this was taken as *a priori* evidence for the presence of antidiuretic hormone.

In many respects their patients resembled the subjects studied by Leaf et al[5] several years earlier. In that study normal subjects were given exogenous vasopressin and developed hyponatremia only when allowed sufficient water intake to go into positive water balance. Natruresis occurred until a new steady state was reached. Administration of vasopressin to subjects on a restricted fluid intake did not result in these abnormalities. Subsequent studies in many other patients with the syndrome have showed the same characteristic relationship between fluid retention, natruresis and eventual development of hyponatremia and hypo-osmolality. In patients with the most severe hyponatremia, however, careful balance studies have not been able to account for the degree of hyponatremia solely on the basis of fluid retention and net sodium loss. It has been suggested that this discrepancy might be explained by osmotic inactivation of solutes.

The mechanism for the natruresis is also of in-

TABLE 1.—*Causes of Syndrome of Inappropriate Antidiuretic Hormone*

Malignancy
Lung
Pancreas
Duodenum
Thymoma
Central Nervous System
Meningitis
Trauma
Brain tumor
Brain abscess
Encephalitis
Guillain-Barré syndrome
Subarachnoid hemorrhage
Subdural hematoma
Acute intermittent porphyria
Central pontine myelinosis
Pulmonary
Pneumonia
Tuberculosis
Cavitation
Positive pressure respiration
Drugs
Vincristine
Chlorpropamide
Clofibrate
Carbamazepine
? Amitriptyline

terest. As a result of volume expansion there tends to be a slight increase in glomerular filtration rate in these patients, although this is not felt to be a sufficient explanation for the sodium wasting that occurs. In addition, volume expansion would presumably result in a decrease in renin and aldosterone secretion. When measured, aldosterone has frequently, but not invariably been subnormal in such patients. Furthermore, this syndrome can be produced experimentally in the face of replacement mineralocorticoids. It is currently presumed that a depression of proximal tubular sodium reabsorption, similar to the mechanism for natruresis in volume expanded animals, accounts for the natruresis in these patients ("third factor").

Recognition of the syndrome depends upon demonstration of hyponatremia and hypo-osmolality of body fluids with urine osmolality inappropriate to the state of hydration. This does not mean that the urine must be maximally concentrated; when steady state conditions are reached the urine osmolality is dependent upon the solute and water intake and may actually be lower than that in the plasma. It has been stressed that excretion of urine that is less than maximally dilute at a time when the body osmolality is subnormal is *a priori* evidence for the presence of antidiuretic hormone. Volume depletion and other nonosmotic stimuli must be excluded since, as we have seen, these can override the osmotic control of ADH. Similarly, the edematous states such as cirrhosis and congestive heart failure are frequently associated with elevated levels of ADH at a time when there is hypo-osmolality; in these patients there presumably is a decrease in effective vascular volume. Normal renal and adrenal function are prerequisites for the diagnosis of SIADH since patients with salt losing nephritis and Addison's disease can present with similar findings.

Other causes of hyponatremia may occasionally be confused with this syndrome, particularly in patients who have had solute loss in excess of water, either through extrarenal routes such as vomiting and diarrhea or via the kidney in patients receiving diuretics. While the fluid loss is usually hypotonic, the replacement is frequently more dilute (that is, water) leading to net hypotonic replacement and a dilutional hyponatremia. The stimulation to ADH may result in an increased urine osmolality, but unless there has been recent access to diuretics, the urinary sodium concentration is often low. This latter finding is also frequent in patients with edematous states who usually can be distinguished on clinical grounds as well. Other syndromes such as glucocorticoid insufficiency and myxedema can be almost indistinguishable from SIADH although in the latter case the mechanism is somewhat different.

The clinical situations that have been associated with SIADH are shown in Table 1. Malignant tumors, most commonly bronchogenic carcinoma, have been frequently reported in association with SIADH. There is now considerable evidence to suggest that such tumors are capable of secreting peptides which are either identical to or very similar to native antidiuretic hormone. A variety of central nervous system lesions have also been described in association with SIADH; presumably there is some interaction with the normal neural control of ADH release. The mechanism is less well understood in the nonmalignant pulmonary lesions although, in at least one patient with tuberculosis, there was evidence of a vasopressin like material in tuberculous lung tissue.[6]

The final category is of particular interest today because in the patient under discussion there may well have been a drug mechanism for the hyponatremia. The list of drugs associated with SIADH is steadily increasing and now includes such di-

verse agents as chlorpropamide, vincristine, clofibrate and carbamazepine. There is no reason to suspect that these drugs have identical mechanisms in causing this syndrome. For example, it appears that the occurrence of the syndrome in patients on vincristine may be restricted to those who have a toxic neuropathy from this drug. Recently increased levels of ADH were found in one such patient[7] and presumably there was some abnormality in the neural control of ADH release.

Perhaps the best studied of the agents has been chlorpropamide. A hyponatremic syndrome which is identical to SIADH can occur in patients receiving this drug and related sulfonylureas. While there is some suggestion that ADH levels may be slightly increased in such patients[8] the bulk of evidence suggests that the mechanism is due to an effect of chlorpropamide to enhance the action of vasopressin on the renal tubule. This is suggested by the fact that the drug has no action in rats with hereditary diabetes insipidus or patients with severe diabetes insipidus but does decrease water excretion in patients with mild pituitary diabetes insipidus. These observations suggest that small amounts of ADH are required for this effect. This is supported by recent studies in toad bladders which have shown a potentiation of the effect of vasopressin and theophylline by chlorpropamide. This direct renal effect is consistent with the observation that the drug has no effect in nephrogenic diabetes insipidus.

At this point we can return to the patient under discussion today. There seems little argument with the diagnosis of SIADH in view of the fact that in this patient there developed profound hyponatremia with associated weight gain, high urine osmolality and inappropriately high urinary sodium excretion with no evidence of dehydration or edema. Renal, thyroid and adrenal functions were subsequently shown to be normal. Proper consideration was given to exclude underlying causes such as occult malignancy or acute intermittent porphyria in view of the history of abdominal pain.

It is attractive to consider the possibility that the syndrome in this patient may have been related to amitriptyline in view of the fact that there has been a recent report of such a relationship.[9] Unfortunately, the patient today has been on other medications as well, although the syndrome clearly developed shortly after amitriptyline was added to the regimen. From an academic standpoint it would have been of interest to challenge the patient with this medication to see if the syndrome was reproducible but the clinicians wisely decided not to take this risk. At present the mechanism relating amitriptyline to SIADH is unknown.

We should close on a note about therapy in such patients. In mild cases simple water restriction will suffice. It is important to remember that some degree of negative sodium balance has occurred and the patient should be allowed access to salt as well. In very severe cases in which the hyponatremia is associated with coma or convulsions it may be necessary to raise the serum sodium rapidly. Administration of hypertonic saline has been the time honored approach. This is, however, potentially dangerous in patients with compromised cardiovascular systems and is only transiently effective since the salt load is rapidly excreted. The technique used in this patient in which furosemide is given in addition to hypertonic saline has recently been shown to be effective and, if proper monitoring conditions can be established, is perhaps the safest way to correct the hyponatremia rapidly.

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Important Advances in Clinical Medicine

Epitomes of Progress—Orthopedics

The Scientific Board of the California Medical Association presents the following inventory of items of progress in Orthopedics. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in Orthopedics which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Orthopedics of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, California Medical Association, 731 Market St., San Francisco, CA 94103

Fiberglass Casts

MANY ATTEMPTS have been made to find an improved substitute for the customary method of external immobilization, the plaster cast. In 1970, Solar Laboratories of California developed a casting material called "Lightcast®." Initially this was a soft fiberglass tape coated with a light-activated resin which activates immediate hardening of the material. The product was subsequently developed further by Merck, Sharpe, and Dohme and marketed as Lightcast II® in April, 1973.

This improved material, currently in clinical use in many offices and clinics, has specific advantages and disadvantages when compared with plaster.

- Advantages: lighter weight (one half to one third of a comparable plaster cast), more durable, radiolucent, can be immersed in water for hydrotherapy or bathing, requires no curing time.
- Disadvantages: increased cost (four to five times higher than plaster), necessity of obtaining and storing a curing lamp, too porous for immediate postsurgical application, technically more difficult and more time-consuming to apply.

As currently marketed, the material consists of a beta fiberglass tape woven in Raschel knit pattern with 3/16 by 3/16 inch openings in the weave. It is coated with a monomer (vinyl toluene) and a polymer (polyester resin), a photo initiator and a photo inhibitor. When exposed to light in the near ultraviolet spectrum (3,200 to 4,000 Angstroms), the photo inhibitor effect is negated, and polymerization becomes complete in approximately twenty-four hours. No studies have been completed on the systemic absorption and toxicity of the monomer, but no cases of toxicity have been reported in the literature.

Durability studies of fiberglass versus plaster by Merck, Sharpe, and Dohme indicate that the fiberglass is superior in impact resistance, abrasion resistance and flexural strength. These tests also indicate that this material is well-suited for casts

and splints that will be subjected to extreme wear and tear, such as with children or heavy laborers. It is also ideal for long-term use because of its durability.

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Surgical Procedures and Hemophilia

RECENT TECHNOLOGICAL ADVANCES with preparation of plasma concentrates of clotting factors have taken the hemorrhage risk out of elective surgical operations on bleeders. Although there are numerous known coagulopathies, deficiencies in Factor VIII (classical hemophilia) and Factor IX (Christmas disease) together constitute the majority of bleeding syndromes encountered clinically. The orthopedist will be consulted for sequelae such as repeated hemarthrosis, joint contracture, destructive joint disease and pseudotumor.

To have considered a surgical treatment for such problems carried great risks in the past. The commercial availability of antihemophilia globulin (AHG), prepared by a variety of methods, and concentrates of Factor IX has altered this. Although the circulating level of Factor VIII required for safe surgery in classical hemophilia has not been established, most authors have advocated raising AHG levels to 100 percent. AHG activity is monitored by the partial thromboplastin time. The duration and level of postoperative therapy is arbitrary; some have allowed circulating AHG activity to decline to maintainance levels of 10 to 25 percent after two or three days. Although the necessary levels may be dictated by the magnitude of the procedure, therapy is usually continued for a minimum of one week.

Nonsurgical means of joint management have been described. The use of intra-articular and oral steroids has been evaluated but results are inconclusive. The management of destructive pseudotumor has been described in a collected review by Schneider. Recently, Storti et al and Ewald et al have described the use of synovectomy as a prophylactic measure against repeated hemarthrosis in juveniles. The destructive effects of this are well known. The problem is universal among hemophiliac children and crippling deformity or ankylosis is the usual sorry result. Knees, elbows and ankles are particularly accessible for surgical synovectomy. An early review of results suggests the incidence of hemarthrosis after synovectomy is much reduced. Ewald has used intravenous and intra-articular epsilon aminocaproic acid to counter local fibrinolysis. This is used for one week in a closed intra-articular irrigation/suction system.

It is hoped that these pioneer efforts will have a positive effect on the long-term management of hemophilia. It is encouraging that the means for safe surgical programs have appeared and early intervention is now possible.

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Implants for Arthritics

THE PAST DECADE has seen rapid changes in the field of orthopedic surgery. Hip and finger joint replacements have become widely used and accepted; knee joint replacements are rapidly gaining in popularity. Other total joint replacement units for the shoulder, elbow, wrist and ankle are currently still in the experimental stage, but are promising.

There are three prototype units for hip joint replacement. But the Charnley type, which utilizes metal to high density polyethylene contact, is proving the most successful. The units are held to bone with polymethylmethacrylate cement.

There are also three prototype units for knee joint replacement: (1) *The hinge*—requires mechanical linkage between the two metal components; (2) *Geometric*—metal to high density polyethylene contact uses two components which furnish a broad area of contact. The components, here again, are held to bone with polymethylmethacrylate; (3) *Polycentric*—metal to high density polyethylene contact uses four components that are cemented into position with polymethylmethacrylate. There are a number of modifica-

tions of these three prototypes on the market. The broad area contact is preferred for patients with osteoporosis and thus is used in many with rheumatoid arthritis. The narrow track type (polycentric) is used for those who have osteoarthritis and little or no osteoporosis. The hinge type is used for those patients whose knees are totally unstable; they seem to have a special place when there is severe posterior subluxation of the tibia. Infection and, therefore, a failure rate of at least 25 percent is expected when hinge knee joints are used.

Metacarpophalangeal Joints

Swanson and Niebauer working independently devised flexible silicone rubber prosthetic devices to be used in these joints. Both have proved satisfactory over the short term, but have yet to be proved in long-term results. The resection arthroplasty first described by Fowler and modified by Vainio and Tupper is still preferred by many experienced surgeons.

Silicone Implants

Silicone rubber implants which are used to replace carpal bones, the distal ulna, the radial head and the base of the proximal phalanx of the great toe after some bunion operations must still be considered experimental.

Investigative Procedures

There are investigations currently being made at several centers in the United States and abroad in an attempt to find suitable units to replace the shoulder, elbow and ankle joints. It is likely that suitable units for these joints will be forthcoming within the next few years. New materials for implants, such as ceramics and new alloys, are also being tested in a number of laboratories.

It is encouraging that interaction between engineering and medicine is providing the basis for new hope for disabled patients with arthritis who may require total joint replacement.

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Spondylolisthesis

SPONDYLOLISTHESIS refers to forward slip of a vertebra onto the one below. We usually think of a defect in the vertebral isthmus (pars interarticularis) which permits the forward slip, but there are several other types of the disease. There is degenerative spondylolisthesis, which frequently occurs in elderly females. Most commonly the fourth lumbar vertebra slips forward on the fifth lumbar vertebra because of degenerative disease, without pars defects. There is also congenital spondylolisthesis which is due to congenitally inadequate bony support. Rarely seen is penduncular spondylolisthesis where there is a defect in the pedicle which permits olisthesis to occur. Isthmic spondylolisthesis is by far the most clinically important in patients under 50 years old. It is never congenital and is never present at birth. The defect is nearly always due to a fatigue fracture with rare cases of acute fracture of the pars due to severe trauma.

Types of Pars Defects

- *TYPE A—Lytic.* This is the common type below age 50. It is due to a fatigue fracture but with a strong hereditary element. These lesions are usually present by age seven but do occur up to adulthood, especially in young male athletes.
- *TYPE B—Elongation of the pars without separation.* This type often shows a high degree of slip. It is due to repeated line fractures followed by healing, permitting slight elongation each time.
- *TYPE C—Aquisita.* This is due to a fatigue fracture in the pars at the top of a posterior spinal fusion. It is very rare now that lateral fusions are being done.
- *TYPE D—Pathological.* Defects occur in the pars in cases of generalized bone disease such as Albers-Schoenberg disease or osteogenesis imperfecta.
- *TYPE E—Acute fracture of the pars.* These are quite rare and occur after major trauma. They will heal if immobilized. It is often difficult to differentiate the acute fracture from a fatigue fracture secondary to repeated trauma such as occurs in the adolescent football player.

About half the cases with pars defects will show forward slip (spondylolisthesis) and the other half will show defects but no slip (spondylolysis).

Treatment

TYPE A—Lytic. In children, if it is believed that the condition has been present for a consider-

able time, one normally treats it conservatively. However, if pain persists, fusion should be done, preferably through the paraspinal approach.

Another reason for fusing in the young child is increasing slip. A slip of 25 percent will just begin to show the typical spondylolisthesis build, a 50 percent slip will produce a cosmetically undesirable stature. With a good solid fusion the tight hamstrings will disappear in several months.

Removal of the loose element alone without fusion should never be done in children.

In adults, the vast majority with spondylolisthesis can be treated conservatively. There is an occasional patient who is brought to surgery because of persistent pain. One need never operate on an adult because of fear of increased slip. In the patient past 60 years old whose principal problem is sciatica, removal of the loose element alone without fusion offers a good chance for relief of pain. Younger people should have a one-level fifth lumbar, first sacral fusion, unless the fourth lumbar level is producing symptoms.

TYPE B—Elongation of the pars without separation. This type is treated the same as type A. Children with this condition are a little more likely to have neurological deficit. Usually only one side is involved in the neurological deficit and need be decompressed by nerve root decompression.

TYPE C—Aquisita. Extension of the fusion is only rarely necessary since most of the time patients with this condition can live with the lesion.

TYPE D—Pathological. No surgical treatment is necessary unless there is slip, in which case the treatment is the same as described for type A.

TYPE E—Acute fractures. These will usually heal if immobilized in a knee-to-nipple cast for about two months. To be sure that the case is acute, the defect must have the appearance of an acute fracture, and one of two things must be present: an x-ray film taken beforehand showing an intact pars, or healing of the pars with immobilization.

Degenerative Spondylolisthesis

The patient should be treated conservatively as long as possible and then decompression is indicated. Often it is not possible to decompress adequately without removing a large portion of the facets. Progression of slip will often occur in these cases. I have seen one case with 33 percent slip before surgery increase to 50 percent after surgery. Fusion should definitely not be done in these older patients. For the occasional patient in his early 50's, a one-segment intertransverse fusion should be done after thorough decompression.

Congenital Spondylolisthesis

The treatment of congenital spondylolisthesis is very similar to that of isthmic spondylolisthesis types A and B. There is forward slip with an intact pars, usually due to insufficiency of the superior sacral facets.

Progressive slip is an indication for fusion. These children are much younger than children with the other types, often as young as 5 or 6 years old. A one-level fusion done through the paraspinal approach will stop further slip.

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The Critical Osseotendinous Junction

IN ATHLETICS in particular, and in certain physical fitness programs in general, the recent emphasis on recreational health, intensive conditioning programs, lengthened seasons for various sports, high level competition and extended athletic careers has increased tendon vulnerability, especially at the osseotendinous junction. Contrary to previous impressions, the area of origin or insertion of a tendon into bone may be involved to a lesser or greater extent. This results in a wide range of conditions: (1) discomfort after activity and no functional disability (phase 1), (2) discomfort during and after activity and no functional disability (phase 2), (3) discomfort during and after activity and significant functional disability (phase 3) and (4) discomfort all the time with significant functional disability or complete tendon rupture (phase 4). These various stages in the development of "tendinitis" have been seen in the swimmer's shoulder, tennis elbow, jumper's knee and achilles tendinitis.

Our incomplete understanding of the underlying pathology and our inability to effectively reverse this process with existing physical therapy modalities or anti-inflammatory medication or both represent basic defects in our approach to these

problems. An added factor of a controversial nature is the repeated injections of steroids into the affected area which may add to weakening of the tendon structure itself. Much research using electron microscopy, histochemical techniques and pharmacological studies needs to be done and may prove especially rewarding. The resort to surgical operation in phase 3 conditions and the development of chronic disability and catastrophic episodes in phase 4 conditions merely emphasize our frustration in dealing with these problems.

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Ambulatory Treatment of Fractures

THE GREATEST SOURCE of disability associated with fractures of the long bones in the lower extremity is the prolonged period of time necessary for bone union to achieve sufficient strength to tolerate the normal stresses of function. An ideal of treatment would be to supply appropriate external support which can allow ambulatory function until sufficient maturation of endoskeletal healing structures has occurred.

The use of ambulatory casts to supply functional support during the healing phase of fracture care has an excellent record of safety and predictable success with 100 percent union rate in significant series of patients. Using these methods, one may expect an average healing time of approximately four months for the tibia and three months for the femoral shaft. The liability of this system, however, is its inability to achieve anatomic reduction and immediate stabilizaton as is feasible with internal fixation methods. On the other hand, skeletal structures are not excessively shielded from the stresses of function and maturation of bony callus can proceed in a most efficient manner.

The use of a cast brace which allows function at the knee by means of appropriate joints applied to the cast enhances the feasibility of early return to ambulatory function. In the case of a femur which has been maintained in skeletal traction until healing phase begins (one to three weeks), a total-contact plaster cast wrapped firmly and tightly at the root of the leg can be applied in the operating room. Closed reduction under general anesthesia is feasible at this time, and appropriate alignment and length can be secured. The specialized cast brace joints may be applied at a later time as appropriate. A cast brace may also be used in conjunction with internal fixation which is of insufficient security to stand the full stresses of function. Using ambulatory casts, rapid mobilization of the patient is reasonable and discharge from acute hospital to home within several weeks of injury should be expected.

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High Velocity Directional Air Flow Systems (HVDAFS)

Status of "Clean Air Rooms"

THE PREVENTION of wound infection is vital to the success of any surgical procedure. This postoperative complication has been an especially tenacious obstacle to the patient and surgeon in achieving successful total joint replacement. Deep sepsis will usually require removal of the prosthetic device.

Among the factors to consider in attempting to effect some control of infection is that the operative and immediate postoperative wound provides an excellent locus for the development of infection; the incidence is also influenced by the number and virulence of organisms present, and the susceptibility of the host. Even the nonpathogenic lower virulence organisms can cause serious deep infections and subsequent prosthetic device removal.

Airbone bacteria are one source of wound contamination which can be controlled. Use of high velocity directional air flow systems (HVDAFS), "clean air" or "laminar flow" in the operating theater have effected a dramatic reduction of microorganisms in the operating room and lower wound contamination rates. Although reduction of airborne bacterial contamination is desirable, the relationship of this reduction to subsequent wound infection has not been definitely established.

The efficiency of these special air flow systems in reducing microorganisms present in the operating room must be placed in perspective with the

inconvenience of their use, for example, the noise and heat, the difficulty in communication, especially with the use of aspiration systems, and the expense of installation and proper maintenance.

The two commercially available types of directed flow units are horizontal and vertical. The horizontal system has the advantage of simplicity and lower cost. Using this system it is possible to provide almost unobstructed purging of the wound for hip surgery, and the overhead lights can be positioned for maximum illumination without obstructing the flow.

During other types of surgical operation such as knee replacement, there is a higher risk of contamination because of the close proximity of the surgeon's face to the wound, and the difficulties encountered by the surgical team as they maneuver to avoid placing themselves between the source of air and the wound.

Using the vertical system, it is virtually impossible to protect the wound from the surgical team unless each member of the team is isolated by an all-inclusive garment and an aspirator or body exhaust system. These isolation systems will also effect further reduction of wound contamination when used with horizontal systems. In addition, the contamination rates using the vertical system are slightly lower than those of the horizontal system, though both are low.

Alternate methods of reducing airborne bacteria in the operating room include reduction of operating room traffic, careful preparation and cleansing of the operating room and wound site, covering all exposed hair and skin, the use of double gloves, impermeable gowns and the use of prophylactic systemic antibiotics.

Several hospitals using prophylactic antibiotics while operating in modern rooms without laminar air flow systems report the occurrence of very low sepsis rates (approximately one percent). In view of these reports, we strongly recommend the use of prophylactic antistaphylococcal antibiotics when doing total joint reconstructive surgery. Antibiotics provide protection within their spectrum not only against airborne contamination in a "clean air" room but from the skin or hematogenous sources. If antibiotics can effect virtual elimination of infections due to organisms found in the operating room then we must consider whether the use of the high velocity flow is necessary.

Airborne contamination is one of several causes of wound infection. Although it is desirable to reduce contamination, reduction in deep wound sepsis has not yet been proven to result from the use of laminar flow systems at operation. We recommend, therefore, that all hospitals where high-risk surgical operations are done evaluate their operating rooms by bacterial air sampling and carefully analyze their surgical results.

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EDITORIAL

Human Health—
A Concern of Medicine

THE CONTINUUM from sickness to health is the business of medicine. The extremes of this continuum are death at one end and well-being at the other, and there is reason to believe that medicine has some expertise to bring to bear even at these extremes. But the traditional emphasis has been on sickness in the form of disease, injury or emotional illness. From time immemorial the aim of physicians and of the medical profession has been to avoid death and to bring patients from sickness to as much health and well-being as possible. Physicians are comfortable when dealing with sickness and restoring health but are somewhat less so when called upon to be experts in health and distinctly less so when it comes to bringing their expertise to the problems inherent either in death or well-being. Yet the entire continuum of death to sickness to health to well-being is the concern of medicine. Moreover, at present the medical profession is under considerable pressure to view sickness from the standpoint of health rather than the reverse—which has been traditional. And one may add that it does not take a crystal ball to foresee that before long medical expertise will be increasingly involved in many new problems pertaining to the extremes of this continuum.

But a new emphasis on health is now clearly being expected and even demanded of the profession of medicine. This has come about subtly and largely because of external pressure. Three forces appear to have played or are playing significant roles. Two of the most important of these forces to date really have little to do with health, while the third—which has only recently come into play—has a direct relation to it.

The first important force appears to have been semantic. Quite simply, while accident insurance was an acceptable phrase, sickness insurance was not nor was death insurance for that matter. Health insurance and life insurance were far more salable phrases, even though they insure neither health nor life. But thought is carried on in the human mind by means of symbols, and these widely used phrase symbols clearly focus thought on health and life rather than on sickness or death. This has already proven to be of no little social, economic and political consequence. And this conditioning, if you will, of the public mind through semantic symbolism seems now to have gone so far as to have reached the point where health and life are very close to being considered the right of every person, to be somehow insured or assured. This, even though the obvious fact is that assuring these conditions can never really be accomplished by insurance, by government regulation or by anything else.

The second force, which also has little to do with health, appears to be the oversell of medical and scientific progress during the past two or three decades. This also has conditioned the public thinking. It has brought about a widespread public belief that health sciences must be capable, and the health care system therefore should be capable, of assuring longer and healthier lives for everyone. A corollary to this is a widely held conviction that more health care will make more people healthy and that more emphasis on prevention and continuing care will not only make more people healthy and lengthen their lives, but will reduce medical care costs as well. These assumptions or beliefs have only partially been borne out in practice. The experience to date, even with massive programs, is that improved health care services have not improved health to any degree near that expected. Nevertheless, health care continues to be an article of public faith, and the public continues to hold the medical profession more or less accountable for any failure to fulfill the public expectations of it.

A third force, which pertains much more directly to health, is only just beginning to be recognized for what it is. There is beginning to be a dim awareness that the problems of human health and survival in the closed earth biosphere are in-

separable from the problems of air, land and water pollution, from the balance of human population with limited food, energy and other essential resources—and that these in turn are inseparable from the continuum of death, sickness, health and well-being which is the business of medicine. The enormity of this force, which focuses directly on what is actually involved in human health, and how it will shape the future of medicine, can only be imagined at this time.

These are some of the reasons why the public emphasis on health and the public expectations from medicine and health care seem here to stay, for the present and foreseeable future. The power of these forces is such that it would be folly to ignore them. It would seem that it is now time for the medical profession to take a new, long and hard look at what is actually involved in health, at what it takes to maintain human health and at how disturbances in human health lead to illness, injury and emotional disorder—as well as the reverse, which has been the traditional approach. If medicine is to continue to serve humanity as it has in the past, it must henceforth make health as much its business as sickness has been. The implications of this for medical education and for the role of medicine in society are considerable but the challenge should be met.

—MSMW

Pathogenesis of Systemic Lupus Erythematosus

THE DISCOVERY of the lupus erythematosus cell phenomenon over twenty-five years ago marked the start of the modern era of research into the pathogenesis of systemic lupus erythematosus (SLE). This initial clinical observation led to the finding of anti-nuclear factor and antibodies to deoxyribonucleic acid (DNA) in the sera of lupus patients. Further studies on renal eluates of lupus patients established the importance of DNA containing immune complexes in the causation of lupus glomerulonephritis, the major cause of death in this disease. As discussed in the paper by Bardana and Pirofsky elsewhere in the JOURNAL, the presence of antibodies to DNA and reduced serum complement have become routine correlates of active systemic lupus erythematosus, distinguishing this entity from other lupus variants.[1]

Although the consequences of antibodies to DNA are clear, the cause of this antibody formation is uncertain. Antibodies to single-stranded DNA occur in drug-induced lupus and other related disorders, and lack the specificity for systemic lupus erythematosus associated with antibodies to double-stranded DNA. Moreover, antibodies to single-stranded DNA can be induced by immunization of experimental animals with DNA complexed to protein and emulsified in Freund's adjuvant. Antibodies to double-stranded DNA cannot be provoked by experimental immunization, and occur almost exclusively in systemic lupus erythematosus and in New Zealand Black (NZB) mice, an animal model for SLE.[2,3]

It is not known whether viral or host DNA is the immunogen for anti-DNA antibodies. As discussed by Bardana and Pirofsky, several lines of evidence favor a role for virus in the pathogenesis of lupus. The presence of antibodies to viral surface antigens, to double-stranded ribonucleic acid (RNA) and to DNA:RNA hybrids is indirect evidence that immunization to viral antigens may be occurring in this disease. Antibodies to double-stranded RNA have a specificity for SLE intermediate between single and double-stranded DNA. They are seen in almost 50 percent of patients with discoid lupus erythematosus and in 70 percent of patients with the systemic disease. They are not necessarily associated with lupus nephritis, and not generally present in the renal immune complex deposits.

An additional antibody activity is also intimately associated with the pathogenesis of systemic lupus erythematosus. Lymphocytotoxic antibodies with specificity for thymic-derived lymphocytes occur in many SLE patients and in New Zealand Black mice. Such antibodies are capable of killing T lymphocytes in the presence of complement and of coating peripheral blood T cells so as to interfere with certain functional activities (such as response in an allogeneic mixed lymphocyte reaction) or with HL-A typing. These antibodies have specificity for T cell surface antigens and can be released from the lymphocyte cell surface in the form of specific antigen-antibody complexes. Such complexes may themselves attach and block other lymphocytes, or may contribute to immune complex deposition leading to vasculitis and nephritis.

A better understanding of the pathogenesis of

SLE has come from detailed studies of the immunologic status of NZB mice at various stages of their disease. These mice are genetically predisposed to the formation of LE cells, antinuclear factor, antinucleic acid antibodies, immune complex nephritis and autoimmune hemolytic anemia.

The overall immune status in SLE and in NZB mice can generally be summarized as an imbalance in which T cell activity is depressed and B cell activity is enhanced.[4] Delayed hypersensitivity responses may be impaired, in part due to the action of lymphocytotoxic antibodies. Antibody formation is both qualitatively and quantitatively excessive, with unusual (that is, autoantibody) and higher titered antibody responses occurring.

Autoantibody formation is normally prevented through the action of T regulatory lymphocytes called "suppressor T cells." Although the mechanism or mechanisms of suppression are unknown, such suppressor T cells probably play a very important role in immunologic tolerance and self/non-self discrimination. A deficiency of T supressor cells has been demonstrated in NZB mice preceding the development of autoimmunity.[5] This deficiency is related to a decrease in concentration of circulating thymic hormone.[6] Administration of thymic hormone to NZB mice can prevent this loss of T suppressor cells and delay the onset of autoimmunity.[5] A reversible loss of T suppressor cells could also explain the drug-induced lupus syndrome seen with procainamide.

As NZB mice age and clinical autoimmune disease becomes apparent, there is a marked loss of various T cell effector functions (for example, response to phytomitogens, ability to induce graft-versus-host disease and ability to reject malignant tumors). Such mice are immunologically impaired and susceptible to infectious agents and to oncogenic viruses. Lymphomas and monoclonal macroglobulinemia are common at this stage.[7-9] Since NZB mice harbor murine leukemia viruses, these lymphoid malignancies may be the final expression of impaired immune surveillance and defective immunologic suppression of viral induced malignancy.

Dubois[1] has emphasized the recent increased death rate from infection and malignancy as deaths from uremia and central nervous system complications have declined in SLE. These clinical observations parallel the experience with NZB mice. Furthermore, malignancy may be potentiated in autoimmune diseases, in renal transplant recipient patients and in NZB mice by the administration of immunosuppressive drugs. Because of this as well as other serious complications, immunosuppressive drugs should be used with discretion in patients with SLE and other autoimmune diseases.

The five-year survival rate in SLE has improved greatly and approaches 80 percent. As we gain understanding of the multifactorial cause of SLE, more rational forms of treatment based on pathophysiologic concepts should evolve. Such concepts may have important implications for oncology and aging as well as for the field of autoimmunity.

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Health Counseling

PRACTICING PHYSICIANS know that large proportions of their patients do not follow their instructions or advice, and public health officials have discovered that much of the public pays little attention to their warnings, dire as these may be. These instructions, warnings and advice all are given with the best of motivation. They attempt to tell the patient or the public what is good for their health. Unfortunately not everyone welcomes or accepts these well-intentioned efforts to tell them what they should do, and compliance—to use a term which is creeping into health care jargon—is considerably less than what is deemed desirable by those who give these authoritative instructions, advice or warnings.

These problems of health counseling have been given less attention than they deserve. It could

be that concern about one's health is an acquired rather than a natural characteristic of humans. After all, the healthy person "feels good" and has no symptoms which draw his attention to his body or its functioning. This is the natural state and this unconcern may be the natural attitude toward health. But concern with one's health can be acquired through losing it or the fear of losing it, or by being convinced on the basis of some logic or other that one should do something in particular to enhance or prolong this natural state. In any case the concern seems to be acquired and in this sense is an unnatural characteristic. Be all this as it may, emotions and feelings are more basic than reason and humans tend to be more emotional than rational in their approach to life. The person who feels well, or who begins to feel well again, is apt to believe everything will be all right and therefore shows poor compliance with health counseling, which usually is telling him he should be doing something he doesn't really want to do. For example, a patient may decide he doesn't need any more medicine or the public will continue to smoke cigarettes, both because they feel well.

All of this has proven to be frustrating to physicians, government officials and others who attempt health counseling. The phenomenon crosses cultural, educational, social and economic lines. There is a clear need for more work to be done on this multifaceted problem. Somehow a rational motivation strong enough to carry the day must be found for whatever health counseling is to be undertaken. Elsewhere in this issue an experience with health hazard appraisal is presented in which there appears to have been substantial compliance with the health counseling which was given. Approaches of this sort may offer some greater promise, perhaps because they set visible goals which are attainable in the present and result in a statistical probability of a longer and healthier life in the future.

—MSMW

CASE REPORTS

Refer to: Denney D, Bigley RH, Rashad AL, et al: Recurrent pneumonitis due to pseudomonas cepacia—An unexpected phagocyte dysfunction. West J Med 122:160-164, Feb 1975

Recurrent Pneumonitis Due to Pseudomonas Cepacia

—An Unexpected Phagocyte Dysfunction

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A PATIENT with necrotizing pneumonitis due to Pseudomonas cepacia (EO-1) was described previously.[1] Two years later at age 21 years, this patient again had severe pneumonia, and Ps. cepacia was isolated from bronchial washings.

The patient's phagocytes ingested but failed to kill Ps. cepacia and several other organisms. The phagocyte dysfunction was indistinguishable from that found in chronic granulomatous disease of childhood (CGD). Most patients with CGD have frequent infections, have multiple granulomatous abscesses beginning early in life, and have a short life span. In the present case, in sharp contrast to this pattern, the clinical course of the patient has been benign.

Materials and Methods

Phagocyte bactericidal capacity was determined by a modification of the method of Quie et al.[2] One milliliter of reaction mixture contained phagocytes isolated from heparinized venous blood and bacteria, in quantities noted in Table 1, suspended in Hanks' balanced salt solution containing 0.1 ml type AB Rh+ serum. After incubation at 37°C (98.6°F) for two hours in a rotating tumbler, 0.1 ml of reaction mixture was diluted with 0.9 ml of distilled water to lyse leukocytes; after culture in pour plates for 12 hours, colonies were counted. Viable organisms remaining in a mixture containing serum, known concentrations of bacteria, and leukocytes before and after two hours' incubation were counted after lysis of cells with sterile water.

Phagocyte nitroblue tetrazolium (NBT) reduction was quantitated by the method of Baehner and Nathan[3] except that instead of fibrinogen for red cell sedimentation, one volume of 6 percent dextran in sterile 1 percent phosphate-buffered saline solution, pH 7.4, was added to ten volumes of blood.

Leukocyte fractionation and enzyme assays were assessed by the methods of Holmes et al.[4] Formate oxidation (H_2O_2 production) was measured by the technique of Holmes, Page and Good.[5]

Some enzyme assays and determinations of NBT reduction were done on blood specimens that had been drawn six to ten hours earlier and transported at airplane cabin temperatures. Activities of control specimens handled in the same fashion were not different from those of fresh normal blood. Normal control specimens were taken from adult laboratory and hospital personnel.

Case Summary

Before age 5 years, the patient had frequent respiratory infections with high fever. On four occasions, brief periods in hospital and penicillin therapy resulted in prompt resolution of fever.

He was subsequently healthy until age 19 years, when pneumonitis due to Ps. cepacia developed. The lungs cleared after several weeks' therapy with chloramphenicol.[1] He was then well until 24 months later when symptoms of upper respiratory infection developed in him and in others in his family. Family members recovered promptly; but the patient had progressively more severe chills,

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fever, cough and pleuritic chest pain. An x-ray film of the chest showed a left lower lobe infiltrate. Treatment for one week with penicillin and cephloridin brought no improvement and he was transferred to the University of Oregon Medical School Hospital.

No other family member has had serious or recurrent infections.

The patient was acutely ill, with a painful nonproductive cough. He appeared well developed and well nourished, and there was no evidence of chronic debilitation. Blood pressure was 112/60 mm of mercury, pulse 120 per minute and regular, respiratory rate 20 per minute, and temperature 40.6°C (105°F). Mucous membranes of the pharynx were dry but not erythematous. Lymph nodes were normal to palpation. The left hemidiaphragm was elevated. Decreased breath sounds and occasional crepitant and fine inspiratory rales were heard over the left lower lung. No friction rub was heard. Results of examination of the heart and peripheral vessels were within normal limits. The liver, spleen and kidneys were not palpable. No skin lesions were noted. Neurological examination results were normal except for slight obtundation and irritability.

The hematocrit was 40 percent and leukocytes numbered 4,150 per cu mm with 63 percent polymorphonuclear neutrophils, 14 percent band forms, 13 percent lymphocytes and 10 percent monocytes. Thrombocytes were present in normal numbers. The urine was slightly cloudy with a pH of 5, specific gravity of 1.023 and 3+ albumin. Microscopic examination showed 5 to 10 pus cells per high-power field and an occasional red cell, but no casts. The blood urea nitrogen was 17 mg per 100 ml and the creatinine clearance was 95 ml per minute. Quantitative urine protein was 100 mg in 24 hours. The serum glutamic oxaloacetic transaminase (SGOT) was 162 units (normal, 15 to 45), bilirubin 0.7 mg per 100 ml, prothrombin-proconvertin 100 percent of normal, and bromsulfalein retention 4 percent in 45 minutes.

Skin tests for tuberculosis, histoplasmosis, coccidioidomycosis and blastomycosis were negative, but normal cellular immunity was suggested by a positive mumps skin test. Cold agglutinins were positive in a titer of 1:32. The patient's ability to form humoral antibodies was shown by the presence of low titers of salmonella Groups C and E, brucella, and Weil-Felix antibodies. Serum IgG was 2,000 (normal, 800 to 1,800), IgA 560 (normal 90 to 450), IgM 90 (normal 60 to 250), and group β_1C complement 570 mg per 100 ml (normal 80 to 140).

An x-ray film of the chest on admission showed an infiltrate in the postero-lateral segments of the left lower lobe. The films were strikingly similar to those taken two years before (Figure 1).

Sputum, nasopharyngeal and blood cultures grew no pathogenic organisms. At bronchoscopy, segmental bronchi of the left lower lobe were observed to be inflamed and edematous, and pus obtained from this area grew Ps. cepacia. Both in its cultural and biochemical characteristics it was similar to the organism isolated from the patient's sputum in 1967. Results of *in vitro* antimicrobial disc susceptibility tests were identical in both isolates. They were sensitive to chloramphenicol and kanamycin, intermediately sensitive to tetracycline and resistant to ampicillin, cephalothin, streptomycin, polymyxin and penicillin. The Ps. cepacia isolated in 1969 was also found to be resistant to gentamicin.

In view of the patient's critical condition and previous response, he was given cloramphenicol, 12 grams a day. Within 36 hours, the temperature had returned to normal. Over the ensuing ten days, chest findings and x-ray showed pronounced improvement. The SGOT and urine abnormalities disappeared. Chloramphenicol was decreased to 6 grams a day on the third day, and to 2 grams a day on the seventh day. This dose was maintained for 24 days, although serum inhibitory activity (SIA) determinations showed no inhibition of growth in undiluted serum. On the basis of disc sensitivity tests, kanamycin was given for ten days (day 22 to 32) but was discontinued because adequate SIA could not be obtained.

We considered use of carbenicillin, a drug known to be active against Pseudomonas organisms. The minimum inhibitory concentration (MIC) determined by the broth dilution method was found to be 6.2 μg per ml and disc diffusion tests showed a zone of 28 mm around a 100 μGm carbenicillin disc. Since adequately high serum levels can easily be achieved with carbenicillin,[6] the patient received 6 grams a day intravenously from day 32 through discharge on day 39.

The patient left the hospital without symptoms and without physical findings of residual lung disease. An x-ray film of the chest showed no abnormality except for scarring and elevation of the left diaphragm as shown in Figure 1.

In follow-up by the patient's family physician to the present time no new findings or subsequent

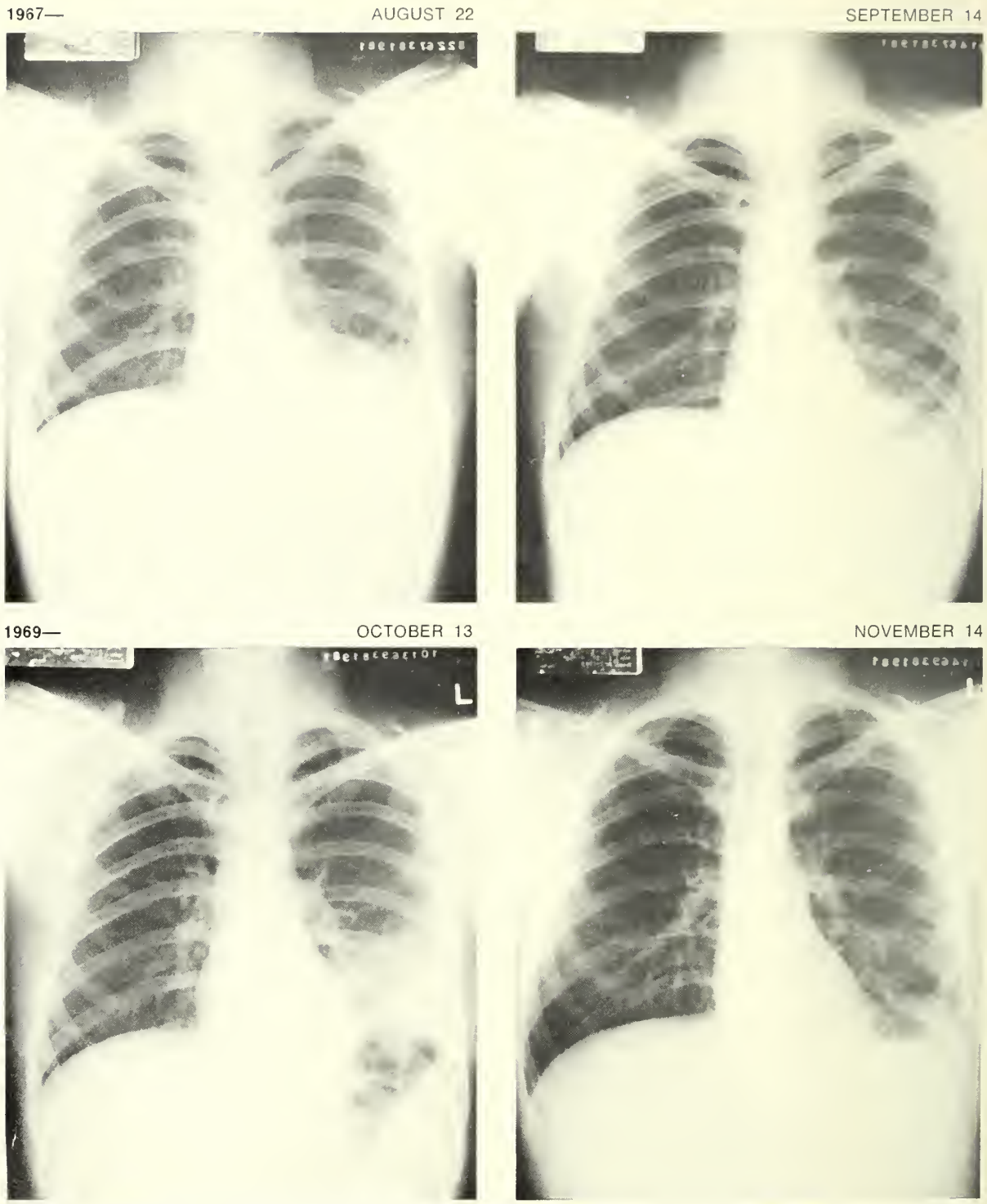

Figure 1.—Admission and discharge chest x-ray films showing similar left lower lobe infiltrates which cleared in each case after chloramphenicol therapy.

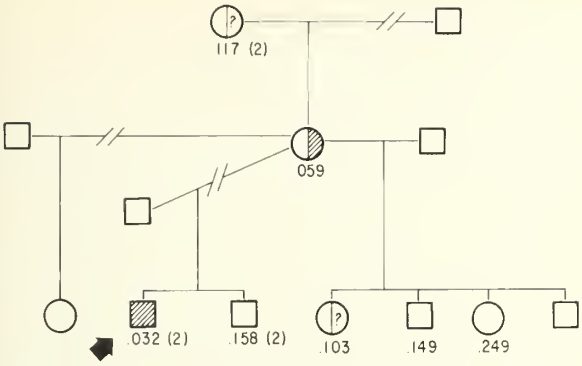

Chart 1.—Family pedigree and nitroblue tetrazolium reduction tests. Patient indicated by arrow. Figures represent net change in optical density $\lambda_{515}/2.5\times10^6$ phagocytes, with number of determinations in parenthesis. Normal controls (N=34) averaged 0.206, range 0.153-0.425. —/ /—=divorce.

serious illness of any kind has been observed. The patient appears to have fully recovered.

Additional Studies

Quantitative NBT reduction (Chart 1) by the patient's leukocytes was decidedly low on hospital day 38, and was unchanged three months later. Values in his mother were intermediate, and those of his maternal grandmother and of a half-sister were near but below the lowest normal values observed in our laboratory.

Bactericidal studies (Table 1) showed that the patient's leukocytes failed to kill Ps. cepacia, Ps. aeruginosa, E. coli and S. aureus.

Phagocytosing H_2O_2 production, measured as formate oxidation, was subnormal (Table 2). Patient phagocytes, incubated with latex alone for 15 minutes, engulfed 5 to 20 particles per cell, showing that phagocytosis was normal. Activities of glutathione peroxidase, glutathione reductase, glucose-6-phosphatc dehydrogenase and 6-phosphogluconate dehydrogenase in the patient's leukocytes were normal.

Review of biopsy material from the lung obtained during the patient's first admission showed necrotizing granulomas (Figure 1).[1] No pigmented histiocytes were found.

After the patient was discharged from the hospital, a second strain of Ps. cepacia highly resistant to carbenicillin was identified in the original culture.

Discussion

It was difficult to decide on the right therapy for this patient. His condition did respond to massive doses of chloramphenicol without serious side effects. However, the severity of illness and the high likelihood that the patient was still infected and susceptible to reactivation of life-threatening disease led some consultants to recommend lobectomy on the infected lung. We elected not to do this because of the likelihood that there was both upper and lower lobe involvement that would require pneumonectomy which could be carried out at a time when he was clinically well. Furthermore, we were hesitant to cross pleural barriers in a patient who had clinically recovered from acute infection.

TABLE 1.—*Comparison of Leukocyte Bacterial Capacity in Patient and a Normal Control*

Organism	*Zero Time Control*	*120 Minutes*	
		Subject Cells	*Control Cells*
S. aureus*	6.3	6.2 (98)	3.5 (55)
Ps. aeruginosa*	3.35	3.3 (98)	1.1 (33)
E. coli*	6.05	5.8 (96)	2.35 (39)
Ps. cepacia (EO-I)†	1.4	0.9 (64)	0.05 (3)

Results expressed as numbers of viable bacteria $\times 10^6$/ml of incubation mixture before (zero time) and after (120 min) incubation. The zero time mixture contained no phagocytes. Figures in parentheses represent percent of zero time control bacteria surviving at 120 minutes.
*1.0×10^6 phagocytes in 1 ml incubation mixture.
†2.0×10^6 phagocytes in 1 ml incubation mixture.

TABLE 2.—*Phagocyte 14C-Formate Oxidation*

	Subject Cells	*Control Cells*
Number of Determinations	2	12
Resting	0.26*	0.46±0.16†
Phagocytosing	0.36‡	1.19±0.28

*Nanomoles $CO_2/10^7$ phagocytes/40 min.
†Mean ± S.D.
‡$p<.005$

Therapeutic concentration of kanamycin could not be achieved, making it an unsatisfactory backup drug should he once again become ill. Carbenicillin appeared promising on the basis of disc sensitivity studies, but SIA was not determined. Even with an adequate serum inhibitory level, the drug may not penetrate into diseased lung and granulomas. Unfortunately, Pseudomonas strains may rapidly become resistant to carbenicillin therapy.[7] Furthermore, we were able to separate a resistant mutant in his original culture, suggesting that, even with adequate tissue levels, survival of organisms remained a possibility. Two recent reports[8,9] demonstrated that combinations including trimethoprim (TMP) and sulfamethoxazole are active against Ps. cepacia. TMP-sulfamethoxazole was used for treatment of Ps. cepacia endocarditis and in one case[9] it was successful in sterilizing the patient's blood and aortic valve.

In the present case, the unusual infections seem

clearly related to the patient's leukocyte dysfunction. His mild clinical course sets him apart from other patients with CGD. CGD is characterized clinically by severe recurrent infections with bacteria which are often of low virulence, widespread suppurative granulomas containing lipid-laden macrophages, and sex-linked inheritance. Clinical variations among patients with CGD have been noted.[10-14] Only one patient, Case 8 of Thompson and Soothill, approaches our patient in paucity of infections.[11] That patient, an 11-year-old boy, had chronic skin sepsis during his first year, a groin abscess at age three years and pneumonia twice at age ten years. Of five patients living to ages 13 to 20 years, all had abdominal visceral abscesses in addition to many other infections.[11-14]

CGD phagocytes have subnormal post-phagocytic increments in H_2O_2 production[5] and NBT reduction.[3] They do not efficiently kill staphylococci and certain Gram-negative bacilli, organisms which produce no net H_2O_2.[15] In these respects, our patient's phagocytes are quantitatively as abnormal as other CGD phagocytes. However, these determinations do not directly measure the activity of the undefined abnormal gene product(s) responsible for CGD. Leukocyte glutathione peroxidate deficiency[4,16] (which is clinically different from CGD only in its autosomal recessive inheritance) and profound G-6PD deficiency are two of possibly several enzyme deficiencies which make up the CGD syndrome.

Variation in clinical and laboratory manifestations of genetically determined disorders is determined by differences in kinds of mutation and in modifying factors, including environment. The causes of clinical variation among patients with CGD and glutathione peroxidase deficiency are not yet established, but extreme variation obviously occurs. Our patient's relatively infrequent severe infections may be due to a less than disastrous mutation. This case suggests that leukocyte dysfunction should be considered in any patient, regardless of age, who has unusual infections.

Summary

Recurrent pneumonitis due to Pseudomonas cepacia (EO-I) developed in a previously healthy patient. Phagocyte bactericidal, peroxide-generating and nitroblue tetrazolium-reducing capacities were decreased. A relatively benign history and the good health of the patient at age 22 years set this case apart from other cases of chronic granulomatous disease.

Addendum

Shortly after this manuscript was submitted, the patient was readmitted to the University of Oregon Health Sciences Center with a recurrence of severe left lower lobe pneumonitis. The history, physical and radiological findings were remarkably similar to those in the previous two episodes. Mild phagocyte dysfunction was again demonstrated. No pathogen could be isolated from sputum, bronchial washings, blood cultures or material from needle aspiration of the lung. In the face of a rapidly deteriorating course, his physicians instituted chemotherapy consisting of cephalothin, gentamycin and carbencillin. Within 36 hours the patient's temperature returned to normal and the pneumonitis resolved rapidly over the ensuing five days. The patient has returned to Alaska and is currently asymptomatic.

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Refer to: Pace NL: Positive end-expiratory pressure (PEEP) in treating salt water near-drowning. West J Med 122: 165-167, Feb 1975

Positive End-Expiratory Pressure (PEEP) in Treating Salt Water Near-Drowning

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THE FAVORABLE OUTCOME of a recent case of salt water near-drowning shows the usefulness of treatment with mechanical ventilation plus positive end-expiratory pressure (PEEP).

Report of a Case

On 13 October 1973, a healthy 34-year-old white mechant seaman fell off his small power boat into Puget Sound. His right wrist was lashed to a trailing rope and he was towed for 30 to 45 minutes behind the slowly moving boat. The water temperature was 12°C (53.6°F). After an unsuccessful helicopter rescue attempt, he was retrieved by a large Coast Guard patrol boat. He was transferred to a Fire Department Aid car. At that time he was comatose, but breathing spontaneously; an electrocardiogram showed atrial fibrillation with a ventricular rate of 80. A venous blood sample was taken (results of later analysis were: sodium [Na] 150, potassium [K] 4, chloride [Cl] 107 and carbon dioxide [CO_2] 9 mEq per liter), and he was given 88 mEq of bicarbonate (HCO_3) intravenously and oxygen by face mask.

Forty-five minutes later, at 16:15, the patient was admitted directly to the Harborview Medical Center intensive care unit (ICU). On initial physical examination the patient was talking and combative though unable to answer questions. He was muscular and his body was a dark purple color, especially the chest, neck and face. Auscultation of the chest showed diffuse rales without gallops or murmurs. On electrocardiogram, rapid sinus tachycardia with frequent premature atrial and ventricular beats was noted. Rectal temperature was 35.2°C (95.4°F) and intense shivering prevented auscultation or palpation of blood pressure. On administration of 100 percent oxygen by nonrebreathing mask the patient was tachypneic, hyperpneic and dyspneic with arterial oxygen partial pressure (PaO_2) 146 torr,* arterial carbon dioxide partial pressure ($PaCO_2$) 51 torr, arterial pH (pHa) 7 and HCO_3 12 mEq per liter (see Table 1).

At this time he was given 132 mEq of HCO_3 intravenously and a muscle relaxant to allow intubation and control of shivering and then was mechanically ventilated with a large tidal volume ($V_T = 1{,}000$ ml) and a high minute ventilation ($\dot{V}_E = 20$ liters per minute). Passive rewarming was allowed and an arterial line placed. A chest x-ray film taken at 16:45 showed bilateral pulmonary edema without cardiomegaly. PaO_2 was now 54 torr on 100 percent oxygen. Because of the large alveolar to arterial oxygen tension gradient ($AaDO_2 = 619$ torr), PEEP 15 cm H_2O was added at 18:00 with improvement of PaO_2 to 145 torr. One hour later, due to a fall of PaO_2 to 114 torr and with continual gross, frothy edema fluid bubbling from the endotracheal tube, a Swan-Ganz pulmonary artery catheter was "floated" and revealed a normal pulmonary wedge pressure of 12 mm of mercury and a normal mixed venous oxygen saturation of 75 percent. PEEP was maintained for about six hours during which gross clinical pulmonary edema and rales disappeared. A chest x-ray film taken at 20:00 showed partial clearing of pulmonary edema. During the evening the patient was incontinent of multiple large watery stools and spontaneously diuresed 1,500 ml by 22:30 (urine electrolytes Na 115 mEq per liter, K 16 mEq per liter). At 02:00, 14 October he was extubated and given humified 40 percent oxygen by mask. Six hours later, immediately before discharge from the ICU, PaO_2 was 77 torr on room air and a chest x-ray study showed dramatic, almost complete clearing of the infiltrates. The only other medication given in the ICU was intramuscularly administered low dose penicillin to prevent pneumonia from aspiration of oral pharyngeal organisms.

The patient convalesced four days on the medical wards until 17 October with a continued spontaneous diuresis and weight loss of 5 pounds. Low dose penicillin was continued; no respiratory care was given other than encouragement to cough and

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*One torr is equal to 1 mm of mercury.

TABLE 1.—*Clinical Course in Case of Salt Water Near-Drowning*

Time	*FiO_2*	*PaO_2 (torr)*	*$PaCO_2$ (torr)*	*pHa*	*HCO_3 (mEq per L)*	*PEEP (cmH_2O)*	*Comments*
16:30	1.0	146	51	7.00	12	0	Intubated, given HCO_3 132 mEq
17:15	1.0	54	40	7.42	25	0	$\dot{V}_E$ 20 liters per min on volume ventilator
18:30	1.0	145	27	7.51	21	15	.....
19:20	1.0	114	27	7.48	19	15	Swan-Ganz catheter placed
21:30	1.0	349	27	7.51	21	15	$\dot{V}_E$ 15 liters per min
23:15	0.35	149	31	7.47	22	15	$\dot{V}_E$ 10 liters per min
00:45	0.35	143	29	7.49	22	0	.....
01:25	1.0	364	34	7.44	22	0	Spontaneous ventilation
02:00	0.4	118	31	7.49	23	0	Extubated
08:00	0.21	77	36	7.44	24	0	.....

FiO_2 = inspired oxygen fractional concentration
PaO_2 = arterial oxygen partial pressure
$PaCO_2$ = arterial carbon dioxide partial pressure
pHa = arterial pH
HCO_3 = bicarbonate
PEEP = positive end-expiratory pressure
V_E = minute ventilation

deep breathe periodically. On a follow-up clinic visit on 24 October 1973, the patient was doing well without complaints. Chest x-ray studies showed minimal perihilar interstitial markings.

Discussion

The major problems following near-drowning with aspiration are hypoxemia and metabolic acidosis.[1,2] The mechanisms of arterial hypoxemia include reflex airway closure[3] and chemical pneumonitis from aspiration of vomitus, algae, mud and so forth.[2] Probably more important, following fresh water aspiration there is damage to surfactant with alveolar collapse and pulmonary shunting.[2] Pulmonary shunting in sea water aspiration comes from flooding of alveoli with a protein rich exudate drawn from the plasma by the hypertonic salt water.[2]

Recent experimental work suggests that PEEP with mechanical ventilation is the optimal pattern of respiration following fresh water aspiration.[4] Equally, in sea water aspiration, PEEP with or without mechanical ventilation dramatically reverses intrapulmonary shunting.[5] Several case reports also suggest its usefulness following both fresh and salt water aspiration.[5-7]

PEEP during mechanical ventilation is the application of positive airway pressure during expiration such that airway pressure does not fall to atmospheric at end expiration. PEEP may be generated by connecting the exhalation port of the ventilator to underwater seal drainage or to a special pressure sensitive valve. (Although a narrowed expiratory orifice will also generate PEEP,[8] creation of dangerously high airway pressures during coughing and straining precludes this method.[9]) Curarization during PEEP is not necessary as there are no significant cardiopulmonary differences between spontaneously triggered mechanical ventilation and controlled mechanical ventilation.[10] There appears to be no increased incidence of barotrauma when PEEP is used as an adjuvant to mechanical ventilation.[11]

Arterial oxygen tension, functional residual capacity and static lung compliance increase[12] and pulmonary shunting decreases[13] with increasing levels of PEEP. Cardiac output and systemic blood pressure may increase or decrease.[12,14] Improvement in oxygenation by PEEP in acute hypoxemic respiratory failure has been ascribed to recruitment of gas exchange airspaces and prevention of terminal airway closure.[12] Careful monitoring is essential to balance the improved gas exchange versus the potential reduction in cardiac output.

A previous large series of salt water near-drownings showed low mortality and morbidity, but the therapeutic management (which included diuretics, HCO_3, intermittent positive-pressure breathing (IPPB), supplemental oxygen and mechanical ventilation only for coexisting respiratory acidosis) allowed hypoxemia and acidosis to persist many hours after admission to the hospital.[1] The aggressive therapy in this patient rapidly terminated severe noncardiogenic pulmonary edema and reduced to a minimum the risks of hypoxemia and acidosis.

As in many other causes of pulmonary edema, PEEP should be considered in the management of salt water near-drowning with aspiration.

Summary

A case of salt water near-drowning is described. Recent experimental work suggests that PEEP is

the optimal pattern of breathing following such an insult. Hypoxemia and pulmonary edema in the patient were quickly alleviated by mechanical ventilation with PEEP.

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Successful Treatment of Non-Meningitic Listerial Brain Abscess without Operation

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THE MOST COMMON MANIFESTATION of Listeria monocytogenes infection in the central nervous system is purulent meningitis or meningoencephalitis.[1] Focal or disseminated suppuration in the brain without meningitis is decidedly rare and only six cases have been recorded in the English literature.[2-7] We report another case of non-meningitic listeriosis with both cerebral and pulmonary abscesses. This case is also unusual in that the patient had a prolonged, relapsing illness and recovered completely without surgical intervention.

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Report of a Case (Chart 1)

A 35-year-old man with polycystic kidneys, chronic renal failure and a cadaveric renal transplant, presented in February 1971 with bilateral diffuse pulmonary infiltrates. Open lung biopsy showed acute, necrotizing bronchopneumonia. Cultures and special stains for aerobic and anaerobic bacteria, fungi, Pneumocystis carinii, and viral inclusion bodies were negative. The patient was nevertheless treated with a trial of pentamidine, penicillin, and cloxacillin. Within two and a half weeks, there was complete radiographic resolution of the pulmonary infiltrates, and he was maintained on prednisone 10 mg and azathioprine 50 mg daily.

In May 1971 he was readmitted to hospital with fever, chills, mental obtundation, expressive aphasia and right facial paresis. Meningeal signs were absent. Consolidation of the apical-posterior segment of the left upper lung was noted. There were no cardiac murmurs or evidence for peripheral embolization. Laboratory findings included hemoglobin of 8.4 grams per 100 ml, hematocrit 23.5 percent, leukocyte count 6,300 per cu mm with 16 percent neutrophils, 83 percent lymphocytes, and 1 percent monocytes, and platelet count

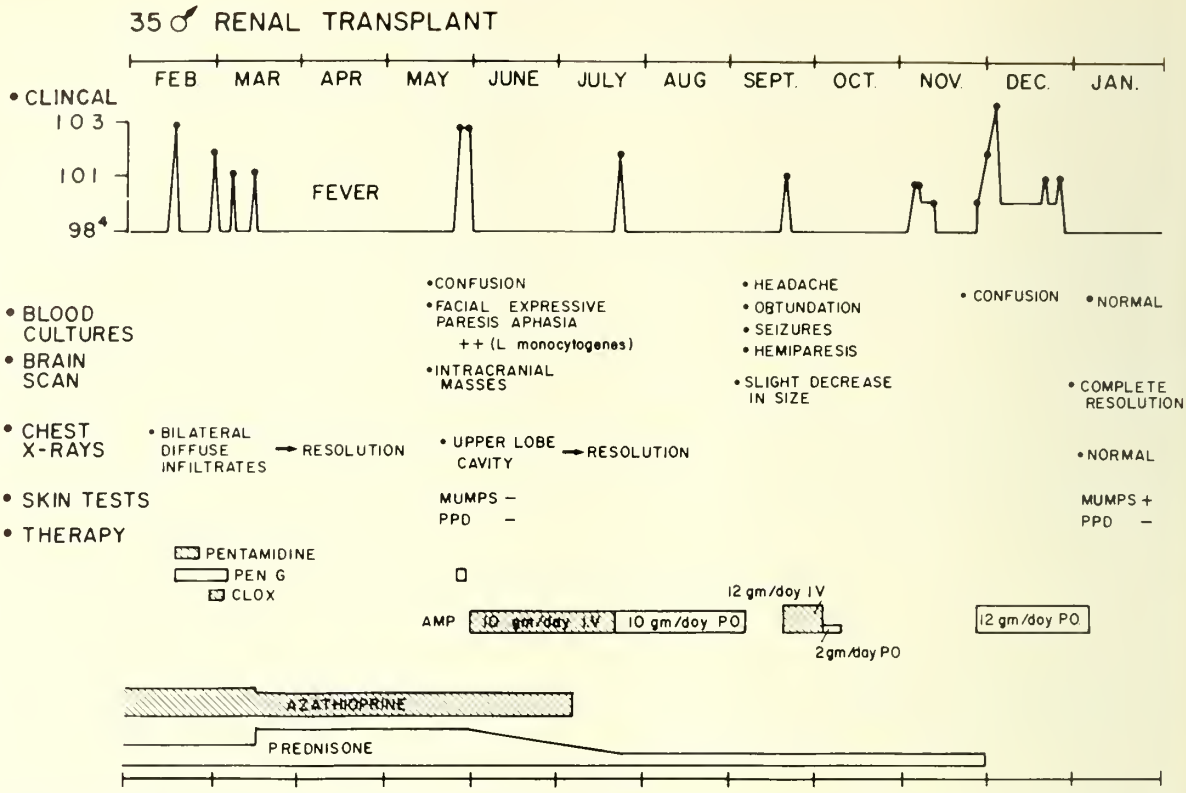

Chart 1.—Clinical course of non-meningitic listeriosis with cerebral and pulmonary abscess in a 35-year-old man following renal transplant.

of 205,000 per cu mm. Blood urea nitrogen was 80 mg and serum creatinine 4.6 mg per 100 ml. Skin tests to mumps antigen, intermediate purified protein derivative, coccidioidin, and histoplasmin were negative. The cerebrospinal fluid was clear, with an opening pressure of 150 mm of water, and contained one lymphocyte per ml with no red blood cells. Protein content was 72 mg and glucose 104 mg per 100 ml. Cultures for bacteria, fungi and viruses were negative. Blood cultures on two consecutive days, however, grew L. monocytogenes serotype la,* sensitive to penicillin, ampicillin, erythromycin, tetracycline, and chloramphenicol. X-ray films of the chest showed an abscess cavity in the left upper lung field (Figure 1), but sputum cultures were negative. Brain scans revealed two space-occupying lesions, each approximately 3 cm in diameter, deep in the left frontal and right frontotemporal regions (Figure 2). A carotid angiogram revealed a slight left to right pericallosal shift compatible with a deep left frontal mass. Because of the deep location and multiplicity of lesions, surgical drainage was not attempted. Azathioprine was discontinued and prednisone was reduced to 5 mg daily. Ampicillin, 2.5 gm every 6 hours, was administered intravenously for six weeks followed by oral therapy at the same dose for another six weeks. The fever rapidly abated and all neurological abnormalities gradually cleared. Subsequent blood cultures became sterile and the pulmonary cavitation resolved three weeks after initiation of therapy.

Two weeks after cessation of ampicillin therapy, however, the patient again complained of fever and severe bi-frontal headaches, followed by a grand mal seizure. On neurological examination, obtundation, minimal nuchal rigidity, right hemiparesis and plantar response in the right foot were noted. The cerebrospinal fluid was again clear, with no cells, and contained 38 mg of protein and 66 mg of glucose per 100 ml. The areas of increased radioisotope uptake previously described on brain scan were slightly decreased in size. There was no clinical or radiographical evidence of recurrent pulmonary involvement. Prednisone was discontinued. Although no pathogens were cultured from blood, urine, cerebrospinal fluid or sputum, recurrent listeriosis was suspected and ampicillin was given again for two weeks, followed

*Confirmed at the State of California Public Health Laboratory.

Figure 1.—Chest roentgenogram demonstrating lung cavitation in apical-posterior segment of left upper lobe.

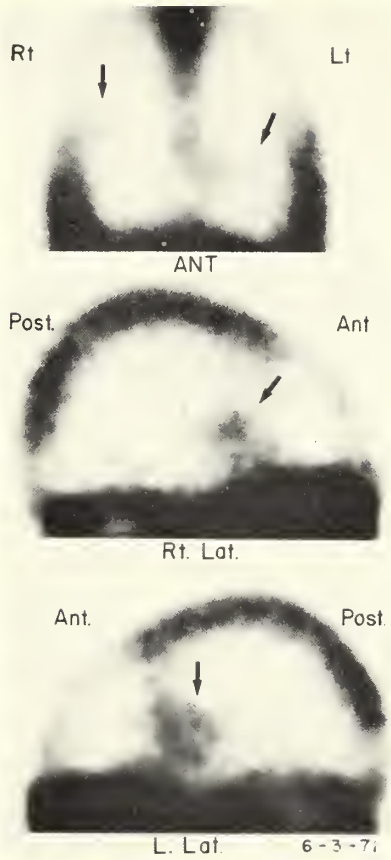

Figure 2.—Brain scans (anterior and lateral views) demonstrating two space-occupying lesions deep in the left frontal and right fronto-parietal regions.

by oral therapy for another week. As before, the fever and neurological abnormalities completely resolved.

In November and December 1971, the patient had further episodes of spiking fever and mental confusion without focal neurological signs. Cerebrospinal fluid findings and bacterial cultures were again negative. Ampicillin by mouth was given again for one month. Clinical response was good and the space-occupying lesions previously demonstrated on brain scan continued to diminish in size. They were completely resolved by January 1972. Concomitant with this resolution, the skin response to re-testing with mumps antigen became reactive. The patient thereafter remained well with no further complications.

Discussion

Focal or disseminated suppuration in the brain without meningeal involvement has rarely been attributed to L. monocytogenes. Since the initial description by Eck in 1957,[8] only six cases of non-meningitic listerial brain abscess or focal encephalitis have been reported in the English literature (Table 1). All patients presented with focal neurological abnormalities without meningeal irritation. The cerebrospinal fluid characteristically was sterile, containing less than 300 white blood cells per cu mm and was otherwise non-diagnostic. Blood cultures, on the other hand, were almost uniformly positive. As with our patient, debilitating underlying disease was present in four of the six cases and corticosteroid therapy was administered in two. Histopathologically, lesions in the brain were characterized by focal necrosis with multiple microabscesses, hyperemia, hemorrhage and perivascular cuffing.[8] Duffy et al[2] and Johnson and Colley[5] also noted extensive fibrinoid necrosis of vessel walls in the affected brain, which suggests the possibility that ischemia of surrounding tissue may interfere with adequate capsule formation in listerial brain abscess. Only one patient survived after multiple antibiotic therapy. A second patient clinically improved after surgical drainage of the brain abscess but died three months later of his underlying disease.

The diagnosis of listerial brain abscess or focal encephalitis in the case here reported, although supported by clinical, radiographical and radioisotopic evidence as well as by concurrent positive blood cultures, was nevertheless presumptive, since bacteriological confirmation of the intracranial lesions was lacking. The possibility of listerial endocarditis with septic embolization to the brain could not be completely excluded. This was unlikely, however, since there was no preexisting heart disease or clinical evidence of valvular involvement. Pulmonary manifestations of listerial septicemia are apparently not uncommon,[1] but have hitherto been underemphasized. In three of the six cases summarized in Table 1 the pa-

TABLE 1.—*Summary of Clinical Data in Reported Cases of Non-meningitic Suppurative Encephalitis or Brain Abscess Due to L. monocytogenes*

Age, Sex	Underlying Disease	Presentation	CSF* WBC (/mm³)	CSF* L (%)	CSF* G (mg%)	CSF* P (mg%)	Culture Blood	Culture Brain	Treatment and Outcome
55[2] ♂	None	Fever, L 6th nerve palsy, Paralysis of R palate and vocal cord, bronchiolitis	183	46	95	53	+	−	Penicillin, streptomycin. Died. Autopsy: suppurative encephalitis pons and medulla, sparing of leptomeninges.
69[3] ♂	Rheumatoid arthritis treated with prednisone	Fever and headache, slurred speech, confusion, L facial paresis, diplopia and nominal aphasia	290	10	60	70	+	−	Penicillin, chloramphenicol, sulfadiazine, ampicillin. Survived with resolution of neurological abnormalities.
49[4] ♂	Rheumatic heart alcoholism and diabetes	Fever, coma, L hemiplegia and ptosis	32	..	72	106	+	−	Penicillin, streptomycin, tetracycline. Died. Autopsy: 2.5× 3.0 cm abscess with thalamus and R corpus striatum; calcified vegetations on mitral valve.
70[5] ♀	Vasculitis treated with prednisone	Fever, coma, L hemiplegia bronchopneumonia	..	..	..	..	+	+	Ampicillin, tetracycline. Died. Autopsy: multiple small abscesses, R frontal and parietal lobes.
53[6] ♂	Cirrhosis	Somnolence and disorientation, L hemiparesis	0	0	75	105	+	+	Penicillin, erythromycin. Clinical improvement following aspiration of right parietal lobe abscess. Died 3 months later of gastrointestinal hemorrhage. Autopsy not performed.
39[7] ♂	None	Headache, L hemiparesis bronchopneumonia	285	70	..	85	−	+	Therapy not specified. Died. Autopsy: small localized brainstem abscess almost transecting the upper spinal cord.

*L = lymphocytes, G = glucose, P = protein.

tients had pulmonary involvement. In the present case, pulmonary suppuration per se could have predisposed to abscesses in the brain.[9]

Until recently, intracranial suppuration without surgical intervention has been thought to be almost universally fatal. Heineman et al[10] and others,[11,12] however, demonstrated that, provided diagnosis and appropriate antibiotic therapy arc established early, intracranial suppuration can be aborted or reversed without surgical intervention. This concept stemmed from Dandy,[13] who believed that, as with furunculosis, inflammation in the brain undergoes several stages, from early, poorly localized, suppurative encephalitis to a well-formed, frankly purulent abscess, with eventual encapsulation. It is believed that this early stage of "immature abscess" is reversible if the infection can be controlled by antibiotics.[14] The experience in the present case, in which antibiotic therapy was initiated within five days of neurological symptoms, appears to support this contention. However, it must be emphasized that the multiplicity and deep-seated nature of lesions in our patient precluded a surgical approach to therapy; and that in the presence of a significant mass effect, reliance on antibiotic therapy alone for well-formed brain abscess is hazardous and is not recommended.

The relapsing nature of illness without changing foci on brain scan in our patient suggests chronic low-grade infection which may have been exacerbated by immunosuppression of the host. In experimental studies involving mice, Louria et al[15] demonstrated that although mortality and tissue census of L. monocytogenes were significantly reduced, adequate doses of penicillin often did not completely eradicate the organism. MacKaness[16] further showed that progressive infection in listeriosis is related to the ability of the organism to survive and grow intracellularly and that acquired resistance is associated with the appearance of cellular immunity. It is perhaps not totally coincidental that clinical recovery in our patient was concurrent with return of cutaneous reactivity to mumps antigen.

Summary

A case of listerial brain abscess without meningitis complicating renal transplantation is reported. The relapsing nature of illness without changing foci on brain scan suggests chronic low-grade infection which may have been exacerbated by immunosuppression of the host. High-dose ampicillin therapy administered over a protracted period resulted in complete resolution of lesions without surgical intervention. This, the seventh case of non-meningitic central nervous system listeriosis to be reported in the English literature, illustrates the importance of early diagnosis and appropriate antibiotic therapy for suppurative intracranial infection.

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Disseminated Coccidioidomycosis

Diagnosis by Needle Biopsy of Liver

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MANY AGENTS produce granulomatous inflammation in the liver.[1-5] Granulomata caused by some infectious agents, such as tuberculosis or histoplasmosis, may have specific morphological features. Autopsy studies have demonstrated the spherules of Coccidioides immitis in the hepatic granulomata of patients with disseminated coccidioidomycosis,[6,7] and there are two reports of the antemortem diagnosis of hepatic granulomata due to Coccidioides immitis.[8,9]

This case of disseminated coccidioidomycosis in which spherules were seen after serial sectioning of a needle biopsy specimen of the liver demonstrates that dissemination of Coccidioides immitis may be found with low serum complement fixation titers. Therefore, liver biopsy is indicated in patients with pulmonary coccidioidomycosis and hepatomegaly or abnormal results of liver function tests even though the serum complement fixation titer is low.

Report of a Case

A 47-year-old black man was admitted to the Los Angeles County-University of Southern California Medical Center with a history of malaise, fever, chills, night sweats, and cough of two months' duration. Although he traveled to Las Vegas, Nevada from Los Angeles, California less than a week before the onset of his symptoms, his home in Northridge, California, an area well known to be highly endemic for Coccidioides immitis, was a more likely site of exposure because the incubation period for primary pulmonary disease is 10 to 14 days.[10] The symptoms persisted

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Figure 1.—Left, the chest x-ray film on the first hospital day showed infiltration in the right upper lobe and an area of consolidation in its posterior segment. **Center,** on the eighteenth hospital day the right upper lobe infiltrations had decreased and a rounded density was forming. **Right,** a film six months after diagnosis showed a coccidioidoma with an area of rarefaction.

despite a course of oral tetracycline therapy. The patient had never been in a hospital before and he denied previous illness or surgical treatment.

On physical examination the temperature was 38.9°C (102°F), pulse rate 110 beats and respiratory rate 16 breaths per minute. No cutaneous lesions or adenopathy were noted. Scattered rhonchi were audible in both lungs. The liver was palpated 4 cm below the costal margin but was not tender. An x-ray film of the chest (Figure 1) showed an infiltrate in the posterior segment of the right upper lobe, and right paratracheal adenopathy.

Laboratory evaluation: hemoglobin, 8.7 grams per 100 ml; hematocrit, 26 percent; leukocytes 15,100 per cu mm with 77 percent polymorphonuclear leukocytes, 10 percent banded forms, 8 percent lymphocytes, 5 percent monocytes, and 0 percent eosinophils; serum albumin, 3.7 grams per 100 ml; serum globulin, 4.7 grams per 100 ml; alkaline phosphatase, 2.9 Bessie-Lowry (BL) units (up to 3.5 is normal); serum glutamic oxaloacetic transaminase, 82 Karmen units (KU) per 100 ml (normal, 8 to 40); serum glutamic pyruvic transaminase, 136 KU per 100 ml (normal, 5 to 35); creatinine, 1.1 mg per 100 ml; blood urea nitrogen, 11 mg per 100 ml; serum iron, 38 μg per 100 ml; iron binding capacity, 196 μg per ml; and saturation, 19 percent; the arterial blood oxygen tension was 80 mm of mercury, and carbon dioxide tension was 31 mm Hg; the pH was 7.45. Gram stained sputum smears showed many polymorphonuclear leukocytes and Gram-positive diplococci.

During the first two weeks in hospital, penicillin was administered but no improvement was noted in the patient's condition. He continued to have temperature rises to 40.6°C (105°F) and lost 11 pounds. Six cultures of sputum were negative for pathogenic bacteria and fungi, and six sputum concentrates were negative for acid-fast bacilli by fluorescent staining. An aspiration needle biopsy of the right upper lobe of the lung was done on the fourteenth hospital day. Spherules of Coccidioides immitis were seen, and intravenous amphotericin B therapy was begun. On the twenty-first hospital day, because of persistently abnormal results of liver function tests and hepatomegaly, liver biopsy was performed. The serum complement fixation titer for coccidioidomycosis (performed by the method of C. E. Smith et al in the Laboratory of LAC-USMC) was 4+ at 1:2 and 2+ at 1:4.[11] The cerebrospinal fluid complement fixation titer was 0 on the 29th hospital day.

The patient's condition slowly improved and after three weeks of amphotericin B therapy (2 grams total dose), he became afebrile and felt much better. The lung infiltrate did not completely clear and six months later a thick-walled cavity in the right upper lobe still remained (Figure 1). Results of serum complement fixation tests for Coccidioides immitis are shown in Table 1. Dissemination is suspected if the titer is 4+ at 1:32.[11]

Pathology

The aspiration needle biopsy specimen of lung obtained on the fourteenth hospital day was fixed in 10 percent buffered formalin, and paraffin sec-

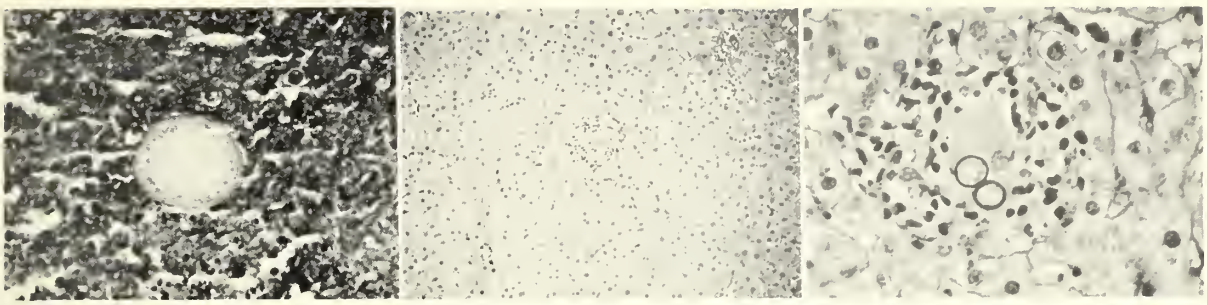

Figure 2.—Left, a Coccidioides immitis spherule containing endospores was found in the lung biopsy material (hematoxylin and eosin stain; X500). **Center,** a granuloma in a midzonal area of a liver lobule (hematoxylin and eosin stain; X100). **Right,** two Coccidioides immitis spherules without endospores within a giant cell in the hepatic granuloma (digested periodic acid-Schiff stain; X500).

tions were made.[6] A Vim-Silverman needle biopsy specimen of liver obtained on the twenty-first hospital day was similarly processed. The sections of lung tissue after hematoxylin and eosin staining showed prominent granulomatous inflammation, microabscesses, and no normal lung structure. The granulomatous inflammation included epithelioid cells, mononuclear cells, multinucleated giant cells, tortuous collagen bands and anthracotic pigment. Many large Coccidioides immitis spherules were identified within the dense granulomatous inflammation. The microabscess formation was characterized by abundant polymorphonuclear leukocytes, necrotic debris and many Coccidioides immitis spherules (Figure 2).

The first cut of the liver biopsy specimen showed normal tissue, but after serial sectioning (25 slides total), a Langhans' giant cell and epithelioid cells were found in a midzonal area in several sections (Figure 2). Periodic acid-Schiff (PAS) staining with amylase digestion revealed PAS-positive rounded bodies in the giant cell, which were approximately the same size as some of the spherules seen in lung tissue (Figure 2). The round bodies did not contain visible endospores and positive identification of Coccidioides immitis cannot be made on histological examination alone. However, since the lung tissue contained Coccidioides immitis, it is reasonable to consider that the giant cell inclusions were Coccidioides immitis spherules.

Discussion

The pulmonary manifestations and sites of dissemination of Coccidioides immitis have been well reviewed by others.[7,12] Most published reports of the morphological features of pulmonary coccidioidomycosis and its dissemination are based on autopsy studies, which indicate that the combination of granulomatous inflammation, microabscess formation, and Coccidioides immitis spherules are diagnostic of pulmonary coccidioidomycosis. All these features were present in this patient.

This case demonstrates that careful search of tissue obtained by needle may be required to diagnose disseminated coccidioidomycosis, when the serum complement fixation titer is low. In the report by Forbus et al of 50 patients with fatal coccidioidomycosis, the liver was the fifth most common organ involved in dissemination.[7] In the autopsy series by Huntington et al[6] of disseminated coccidioidomycosis, almost 50 percent of the patients had liver involvement. However, in the report by Klatskin[1] of 29 patients with hepatic granulomata diagnosed by needle biopsy, none was due to coccidioidomycosis. Another series of granulomatous hepatitis cases from areas near those endemic for Coccidioides immitis showed no coccidioidomycosis of the liver among 63 patients.[2] There are two case reports of antemortem diagnosis of hepatic coccidioidomycosis. In one report, a young male patient with persistent fever (two months), leukocytosis, and eosinophilia was found to have multiple hepatic granulomas containing Coccidioides immitis spherules. Five days later, the coccidioidomycosis serum complement fixation (CF) titer was positive at a dilution of 1:256.[8] In a second report,[9] a young woman had jaundice, persistent fever, and hepatomegaly; a needle biopsy specimen of the liver showed hepatic granulomas containing Coccidioides immitis. The coccidioidomycosis serum complement fixation titer was 4+ at a dilution of 1:8 and 3+ at 1:16.

In most patients with disseminated coccidioidomycosis, the serum CF titer is greater than 1:32.[12] However, Smith et al have found that up to 15 percent of patients with disseminated coccidioidomycosis have maximum serum CF titers of 1:16 or

less. In the present case, the serum CF titer was 4+ at a dilution of 1:2 at the time the hepatic granuloma was demonstrated (July 27, 1972, Table 1). Therefore, a low serum CF titer does not exclude dissemination. Subsequent serum CF titers rose to 4+ at 1:32 dilution which is indicative of possible dissemination.[12] It is conceivable that in other cases of pulmonary coccidioidomycosis, dissemination may occur and go undetected if a single serum CF titer is obtained. Therefore, in patients with coccidioidomycosis and low serum CF titers (below 1:32), hepatomegaly or abnormal liver tests are indications for needle biopsy of the liver. Furthermore, culture of the liver biopsy material is recommended, though unfortunately it was not done in the present case.

In the patient presented, the liver biopsy was first reported as normal, but because of the suspicion of dissemination of coccidioidomycosis, serial sectioning of the specimen was done. It is recommended, therefore, that the tissue be thoroughly examined before concluding that hepatic granulomata are not present.

Summary

A patient after a two-month illness was diagnosed by lung biopsy to have pulmonary coccidioidomycosis. Because the SGOT and SGPT were elevated (82 and 136 KU/100 ml respectively) and the liver was enlarged, a needle biopsy specimen of liver was obtained. Serial sectioning of the liver tissue demonstrated hepatic granulomata containing Coccidioides immitis, although the serum complement fixation titer did not indicate dissemination. It is suggested that needle biopsy of liver might reveal that dissemination of coccidioidomycosis is more common than is recognized by serum complement fixation titer.

TABLE 1.—*Results of Serum Complement Fixation Test for Coccidioidomycosis*

	DILUTION							
Date	1:2	1:4	1:8	1:16	1:32	1:64	1:128	1:256
7-27-72 (Hospital day 21)	+4	+2	0	0	0	0	0	0
8- 9-72	+3	+3	+2	+1	0	0	0	0
11- 1-72	+4	+4	+4	+4	+4	0	0	0
12-27-72	+4	+4	+3	+2	0	0	0	0

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LETTERS *to the Editor*

Myelomeningocele

To the Editor: In the October, 1974, issue your journal carried an excellent symposium on myelomeningocele [Specht EE, Goodner EK, Tanagho EA, Prince B, Pevehouse BC, Cohen P: Myelomeningocele—A symposium on orthopedic, ophthalmologic, urologic, psychological and social, neurosurgical and general considerations (Pediatric Rounds). West J Med 121:281-304, Oct 1974]. It was noted in passing in the article by Dr. Cohen that there was a sixfold [recurrence] risk [of spina bifida cystica in a family after the birth of one such disabled child] compared with that in a normal family. Actually the recurrence risk appears to be 4 to 5 percent. It was not mentioned, and I feel it should have been, that because of this recurrence risk and because of the emotional components of having a disabled child, genetic counseling is often appropriate for these families. This, of course, requires that the physician caring for the patient thinks of this and is familiar with the local availability of such counseling. Also, I was somewhat disappointed that, although it has been two years since Brock and Sutcliffe reported the association between increased alpha-fetoprotein levels in the amniotic fluid and the presence of a fetus with a neural tube defect (Lancet 2:197, 1972), this relationship was not mentioned. It has since been firmly established that determination of the amniotic fluid alpha-fetoprotein level between 15 and 20 weeks of gestation makes possible the prenatal detection of neural tube malformations. I think that the possibility of such prenatal detection must be explained to each family with a child with a neural tube defect.

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* * *

To the Editor: I have read the myelomeningocele symposium published in the October, 1974, issue of The Western Journal of Medicine. In discussing the neurosurgical management of these cases, I think Dr. Pevehouse failed to emphasize the most important reason for closing a myelomeningocele, which is preservation of neurological function.

Anyone who has witnessed the delivery of children with myelomeningoceles will note that frequently the lesion is very flat upon delivery and the sac is unbroken. This is because intrauterine pressure keeps the neural tissue and the contents of the myelomeningocele in relatively proper position. Once the child is delivered, the atmospheric pressure is lower than the intrauterine pressure and the lesion expands. With the expansion of the lesion, increasing neurological deficit may occur, even though the child may seem neurologically intact at birth.

I would emphasize that closure of most myelomeningoceles is a true neurosurgical emergency and should be done as soon as possible after birth. If this is not feasible, some type of hyperbaric unit to enclose the lesion could be employed to keep the neural elements in anatomical position until definitive surgery can be performed.

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Screening Without Meaning

To the Editor: Entry of the Brown Bill (AB 2068) into the California Health and Safety Code as Chapter 1069 establishes a legislative and fiscal basis for implementing federally mandated Early and Periodic Screening, Diagnosis, and Treatment (EPSDT) of children. Concerned physicians have emphasized that screening in the absence of a regular source of health care may be of no benefit to the patient (for example, Gershman M: Position on early and periodic screening [Letter to the Editor]. West J Med 121:69, Jul 1974). At the other end of the spectrum, when adequate care is being received through an established patient-provider relationship, an isolated screening program may do the patient a disservice by introducing duplication, with its attendant confusion and fractionation.

From the economic standpoint, AB 2068 requires development of community record systems "so that costly and unnecessary repetition of

screening will not occur." The following is an example of expensive duplication and fractionation of services, resulting from a well-intentioned screening effort that was not coordinated with existing arrangements for care.

Several pediatricians in this medical group received identical communications stating that patients regularly under their care had been enrolled in a medical screening project sponsored by a local school district, and that unless objection was received (in some instances within two days after the notice arrived), the patients would be scheduled for screening examinations. The program's medical consultant, who would "evaluate the child's need for care," was found to be a resident in pediatrics at a local medical center, which offered postscreening care to the participants "at clinic rates." Ironically, the children chosen for this isolated screening had been receiving continuity of care as members of a prepaid program which has long utilized multiphasic testing for children and adults[1,2] as part of a comprehensive health care system.

In 1973 Hass[3] urged that EPSDT not become a self-contained, isolated system, and outlined a practical method for fitting it within the scope of regular and continuous pediatric care. One approach would be to group the children of a given state into three categories. (1) Those already receiving care that meets or exceeds EPSDT requirements. For them, the provider might be required only to submit essential statistical data. (2) Children eligible for Medicaid who live in areas where care meeting EPSDT criteria is available, but not to them. Here, public welfare efforts could be directed toward identifying such children, interesting providers in seeing them and getting them to the providers. (3) Children living in areas that lack sufficient providers. For these, publicly supported programs might well make arrangements for screening, possibly through schools, and encourage providers to cover such districts. The last two needs cannot be met without adequate funding.

If EPSDT needlessly disrupts existing systems, duplication and expensive chaos can be anticipated. Laws mandating screening have been passed in the absence of evidence that screening programs in themselves can have a positive effect on health care. One of the greatest dangers of an isolated testing program is that screening could become an expensive and rigid goal in itself. Continuity of care is more important than specific screening tests. If screening is to have any meaning, it must be within an ongoing health program for the patient.

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Refer to: LaDou J, Sherwood JN, Hughes L: Health hazard appraisal in patient counseling (Preventive Medicine). West J Med 122:177-180, Feb 1975

Preventive Medicine

Health Hazard Appraisal in Patient Counseling

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A program of annual health examinations was expanded to include counseling based on a computerized appraisal of individual patients' specific health hazard factors. Data obtained from a specially designed questionnaire, laboratory tests and a physical examination yielded a printout showing a number of weighted risk factors and their relation to ten leading causes of death as determined for that patient. From all of this information, a risk ("apparent") age was developed for the patient. The results were reviewed with each patient, and methods of correcting health hazards were stressed. A total of 488 persons were appraised, and 107 were randomly reappraised in less than a year, with the finding that the net risk age was reduced by 1.4 years. Such a reduction in risk age is significant; it indicates that appraisal-based counseling is an effective method of altering priorities of health practices.

HEALTH HAZARD APPRAISAL has been proposed as a method of outlining a preventive medicine program under the comprehensive care of the physician.[1] The principle is based on the fact that each person is faced with certain quantifiable health hazards as a member of a sex-age-race constituted group and, further, that these average risks may be applied to a patient if the clinician knows the patient's prognostic characteristics and the mortality experience of cohorts with similar prognostic characteristics. The proposal that early intervention of disease be accomplished through recognition and reduction of specific risks has been advanced by many proponents of prospective medicine.[2-5] The study discussed here was conducted to determine the impact of health hazard patient counseling on risk reduction.

The health hazard appraisal is a method of using information from a patient's medical history, physical examination and x-ray and laboratory data to quantify his risk of death in an ensuing ten-year interval. The degree of risk is determined using tables that indicate the likelihood of death from specific causes for the average United States population. These tables, which are based on actual mortality data, were developed by Harvey Geller of the United States Public Health Service.[6,7] For every cause of death, the health hazard appraisal printout displays a set of weighted factors that may alter the prognosis of death from specific causes in either a positive or negative way. Typical factors of importance are blood pressure, weight and smoking habits for

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TABLE 1.—*Ten-Year Mortality (Geller) Table for a White Man, Age 45*

Rank	Cause of Death	Chance in 100M of the Person Dying from This Cause
1	Arteriosclerosis, heart disease and chronic endocarditis	3,507
2	Malignant neoplasm of lungs	486
3	Vascular lesions of central nervous system	428
4	Cirrhosis of liver	370
5	Suicide	313
6	Motor vehicle accidents	313
7	Chronic rheumatic heart disease	220
8	Pneumonia	185
9	Malignant neoplasm of intestines and rectum	185
10	Other disease of the heart	150
11	Malignant neoplasm of stomach and esophagus	150
12	Hypertensive heart disease	150
13	Lymphosarcoma	93
14	Tuberculosis	93
	Other causes	2,524
	TOTAL CAUSES	9,200

heart disease; and mileage, alcohol and seat-belt use for automobile accidents. In this way, the outlook for each person is assessed against the "average" risk of death in the next ten years, from each cause, with specific prognostic altering that risk above or below the average.

Individual risk factors have been developed for each prognostic characteristic identified from the prospective studies in Framingham;[8] the study of cigarette use and lung cancer by Hammond and Horn[9] and numerous studies made by the health insurance industry, medical schools, hospitals and government agencies.[10,11] The resulting data were used to develop a system of prospective medicine and to prepare a risk factor manual (available to physicians from the Methodist Hospital of Indiana, 1604 North Capital Avenue, Indianapolis, Indiana 46202, or as a computer processed report from Interhealth, 2970 Fifth Avenue, San Diego, California 92103).

Table 1 is a Geller Table for an average 45-year-old white man in the United States. He has 9,200 in 100,000 chances of dying in the next ten years, with the highest risks being from heart disease, lung cancer, cerebrovascular accident, cirrhosis and suicide. Application of the risk factor manual to these data is demonstrated by the following example. If this man smokes one package of cigarettes per day and does not use alcohol, his overall risk would be increased to 11,000 in 100,000 in the next 10 years. Hence, his risk is no longer that of a 45-year-old man, but similar to that of a 47-year-old man. Although abstaining from alcohol decreases his risks, smoking has resulted in a proportionately greater increase in risk of death—almost 2,000 chances in 100,000 more than an average person of his age. More important, if he stopped smoking, he could reduce his risks by 26 percent, giving him the risk factor of a 44-year-old man. With such information, patients can be made aware, in a quantitative way, of their risks and can begin a meaningful program to effect changes.

Methods and Background

Ames Research Center is the employer of 1,600 National Aeronautics and Space Administration personnel at Moffett Field, California. The average age of this population is 44. The majority of these workers participate in an annual health examination program given at the Ames Health Unit. Examinations include chest x-ray and electrocardiographic studies, submaximal stress electrocardiographic testing, laboratory profiles, physical examinations and health hazard appraisal.

For the health hazard appraisal, the examinee answers the questions in a six-page booklet, including questions regarding life-style, known diseases, family history, habits, emotional status and racial background. Physical data are inserted by Health Unit personnel, and the booklet, identified only by initials and a number, is forwarded to a central facility for analysis by a computer. Each patient is seen in a follow-up consultation two weeks after examination, and the results of the various tests are explained in full. During the interview, the physician discusses those factors relative to death risks that vary significantly from the norm. These data are summarized for the patient by a comparison of *present age* with *risk age* (as determined by the health hazard appraisal).

Changes in life-style or habits or the need for specific treatment are outlined where appropriate, and the patient is urged to consult his own physician, to whom a copy of all records is sent. The effects of compliance with recommended changes in life-style, such as the institution of exercise programs, weight loss, discontinuance of smoking and modification of alcohol use, are presented to the patient as a *potential age* to demonstrate the benefits of risk reduction.

At the time of this writing, 488 persons had

PATIENT NAME: MC DATE: 09-20-73

DOCTOR NAME: Ames Health Unit PATIENT ID: 000097747 M

AVERAGE	Risk/100,000	5,490	PRESENT AGE	40
PRESENT	Risk/100,000	2,936	RISK AGE	36
POTENTIAL	Risk/100,000	2,652	POTENTIAL AGE	33

NOTE: The patient's risk may be increased by the following hazardous avocation: Drives motorcycle

CAUSE: Accidents, Motor Vehicles

AVERAGE RISK	339 (1.0)
PRESENT RISK	305 (.9 x Avg)
POTENTIAL RISK	108 (.3 x Avg)

CONTRIBUTING FACTORS	Present Risk	POTENTIAL RISK WITH TREATMENT	
Alcohol: 1-2 drinks/wk	1.0	None before driving	.5
Mileage - 10,000	.8		
Seat Belts: less than 10% usage	1.1	Always use seat belts	.8
Drives motorcycle			

CAUSE: Arteriosclerotic Heart Disease

AVERAGE RISK	1,861 (1.0)
PRESENT RISK	130 (.1 x Avg)
POTENTIAL RISK	74 (.1 x Avg)

CONTRIBUTING FACTORS	Present Risk	POTENTIAL RISK WITH TREATMENT	
B.P. (Avg) -- 122/080	.4		.4
Chol (Avg) -- 180 Mg%	.5		.5
Exercise: some activity	1.0	Exercise as directed	.5
Smoking: nonsmoker	.5		.5
Weight - 06% overweight	.8	Reduce to average	.8

CAUSE: Cirrhosis of Liver

AVERAGE RISK	304 (1.0)
PRESENT RISK	61 (.2 x Avg)
POTENTIAL RISK	30 (.1 x Avg)

CONTRIBUTING FACTORS	Present Risk	POTENTIAL RISK WITH TREATMENT	
Alcohol: 1-2 drinks/wk	.2	Stop drinking	.1

Figure 1.—Health hazard appraisal computer printout for a 40-year-old white man.

been counseled in this manner. Of these, a random group of 107 were given repeat appraisals within a year, and the results—capsulized as the risk age—were compared with the first appraisal.

Figure 1 shows an Interhealth computer printout for a 40-year-old, white man. The average risk of death in the next ten years, as derived from the Geller tables, is 5,490 chances in 100,000. Because of favorable health practices and medical history, however, his risks are significantly reduced. The present risk of 2,936 in 100,000 is derived from the health hazard appraisal and is equated to a risk age four years less than his present age. Compliance with the various recommendations shown in the right-hand column of the printout would decrease this person's risk to 2,652 in 100,000, and offer him a potential age of 33. Information such as this has been used to develop the Ames Health Unit system for patient counseling for risk reduction.

Results

The first 50 patients were timed as they completed the health hazard appraisal test booklet. The testing time ranged from 11 to 24 minutes, with an average of 17 minutes. Seven out of 495 patients refused to participate in the program. Occasionally, patients left questions unanswered, but all those participating consented to the use of average values for the omitted areas to allow the remainder of the health hazard appraisal to be evaluated.

Averages of the results of the Ames health hazard appraisals are shown in Table 2. The close approximation of average *present age* and *risk age* indicates the similarity of the Ames Research Center group to the larger United States popula-

TABLE 2.—*Average of Health Hazard Appraisal Results for the Ames Research Center Population*

Number of Patients	*Present Age*	*Risk Age*	*Potential Age*
488	48.45	48.37	43.45

TABLE 3.—*Average of Health Hazard Appraisal Results of 107 Examinees Evaluated on Repeat Periodic Examination*

	Present Age	*Risk Age*	*Difference (between present and risk ages)*	*Potential Age*
Initial HHA ...	49.43	49.56	+0.13	44.69
Repeat HHA .. (N=107)	50.06	48.66	−1.40	44.34

tion. However, the standard deviation of *risk age* from *present age* is 4.24 years. In those cases where risk age was greater than present age, this deviation would suggest an added value in patient counseling. For the group of 488, the average *potential age* is fully five years less than *present age*. This finding reinforces the value of patient counseling.

The value of the health hazard appraisal in motivating patients to improve their health practices can be assessed by comparing the average variance of present age with risk age between initial testing and annual retesting. In the Ames Health Unit, 107 patients have been retested and the results are shown in Table 3. For these patients, risk age was found to be 0.13 years greater than present age in the initial health hazard appraisal, but 1.40 years less than present age in repeat testing. This difference is highly significant, with a "p" value less than .001. It represents an average of 32 percent of the difference between present age and potential age. The potential age for this group when retested remained five years less than risk age.

A questionnaire was used to assess patient acceptance of the health hazard appraisal. Eighty percent of a sampling of 162 persons indicated full acceptance of the program and a desire to be retested annually. Half of the subjects interpreted their test results as indicative of a need for change in their health practices. Eighty percent indicated their intention to make some or all of the necessary changes to achieve a lessened risk of death in the next ten years.

Comment

Mortality statistics would appear to provide an unlikely means of patient counseling in health practices. The opportunity to alter the risk of death on a ten-year prognostic basis, however, is a dynamic function of compliance with patient counseling. The physician has learned that statistical probabilities put various risk factors into an order of priorities that is easily understood by the patient. The importance of seat belts as compared with exercise, weight control and other health practices tended to add to the total value of patient counseling by adding subject material frequently considered by physicians to be outside the field of medicine. The degree of patient acceptance of the health hazard appraisal was illustrated by the compliance of the group undergoing periodic retesting and by their willingness to repeat the health hazard appraisal annually.

Health hazard appraisal will become an increasingly important adjunct to patient counseling as risk factors are further quantified. The addition to health hazard appraisal of risk factors such as personality typing and the impact of social changes on future health will be important developments.

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Refer to: Chesbro WP: The role of medicine in aviation safety (In the Forefront). West J Med 122:181-182, Feb 1975

The Role of Medicine in Aviation Safety

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THE JULY 1969 issue of CALIFORNIA MEDICINE (Vol. 111:55-56) carried an article entitled "The Role of Medicine in Aviation Safety." Since that initial statement, significant progress has been made and continues to be made. The following is a report of that progress.

The California Aviation Safety Council

In April 1968, while participating as a panel member at a Congressional hearing in San Francisco on the subject of aviation safety at carrier airports, I was appalled at the lack of basic emergency equipment as well as the inadequacy of disaster planning for mass casualty care. Of the 37 major carrier airports in the United States, only two had a 24-hour emergency medical facility, and none had held a test exercise to demonstrate the adequacy of their disaster plans.

Further discussion showed that no coordinating body existed in the state of California to deal with the problem of aviation safety. To explore the need for such a body, two symposia on the medical aspects of aviation safety were held under California Medical Association auspices in 1968 and 1969, with approximately 100 people attending in each instance. Participants were carrier pilots, physician pilots, aviation medical examiners, cabin attendants, airport executives, airport fire and police components and personnel concerned with disaster planning on a governmental level. The enthusiastic interest of the participants in the medical aspects of aviation safety was sufficient to warrant the formation of a nongovernmental council on aviation safety. In February 1970, initial meetings were held with over 20 representatives of all aspects of aviation concerned with safety. In 1971 a constitution and bylaws were accepted, and the California Aviation Safety Council was formed. Active members were:

- Air Line Pilots and Stewardesses Association
- California Medical Association
- California Fire Service
- Air Traffic Control Association
- Aircraft Pilots of Metropolitan Oakland
- Airport Executives Representatives
- The Ninety-Nines, Inc.
- The Sierra Academy School of Aviation Instruction
- California Crop Dusters Association
- California State Department of Aeronautics
- California Highway Patrol
- Office of Emergency Services
- Armed Forces Representatives
- California Peace Officers Association
- Federal Aviation Administration, Western Regional Representatives, Los Angeles

Changes and additions have been made in the foregoing according to interest expressed by these professional organizations.

Purpose and Objectives

The purpose of this council is to promote, among its members, all measures devoted to passenger safety in aviation.

The most immediate deficiency found was the lack of adequate disaster planning in the event of mass casualties from aircraft accidents at carrier airports, and action to remedy this problem was our first objective.

Carrier Airport Disaster Planning

Four years ago there were no significant disaster plans for mass casualty care at any carrier airport in California. One of the smaller carrier airports

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Submitted revised July 25, 1974.

Reprint requests to: W. P. Chesbro, MD, California Aviation Safety Council, 731 Market Street, San Francisco, CA 94103.

had held a test exercise. In May 1971, the first simulated mass casualty disaster test exercise was held at Oakland International Airport. Using 110 simulated casualties evacuated from an aircraft, supportive care was given in all phases from the collection site 500 feet upwind of the aircraft to transportation and care at the airport casualty collection center, with further air and ground transportation to the peripheral receiving hospitals for final definitive care. Problems in removal of casualties from a crowded aircraft cabin interior, the adequate means of casualty transportation to the airport stabilization casualty support facility, the jam-up of casualties because of poor "flow through" patterns at the facility, the proper coordination of transport, and the medical channel communications from disaster site to final hospital facility—all were present, well-illustrated and recorded. In August 1972, San Francisco International Airport held the second large test exercise. The same problems appeared, as well as some new ones. In October 1972, Los Angeles International Airport held the third large-scale test exercise, with some of the errors found in the two previous exercises appearing again.

Changes in plans and equipment used for disasters are being made at all three airports based on knowledge gained from actual demonstration of their worth. Members of the California Aviation Safety Council either directed or participated in all three exercises.

The most active support organization to the council has been the Air Line Pilots Association, represented by Captain John X. Stefanki, Vice Chairman of the Council. Captain Stefanki, through his national contacts, has urged other states to form similar councils. During the past year he has also acted as an advisor to many large carrier airports in the United States holding test exercises of their disaster plans.

Emergency Medical Facilities

It is the feeling of the California Aviation Safety Council that any carrier airport used by more than two million passengers annually and with at least three thousand employees should have an established emergency medical facility. At present, a study is underway toward classifying the staffing of airport emergency medical facilities based on the number of passengers using the airport and the number of employees. San Francisco International Airport during the past year has established an excellent daytime emergency medical facility whose coverage will extend as necessary. The situation is different, however, in some other airports. It is interesting to note, for example, that Chicago's O'Hare International Airport, with one of the largest passenger and employee levels in the world, has no physician-staffed emergency medical facility.

National and International Goals

The California Aviation Safety Council has urged, through its members representing national organizations, the establishment of state councils of aviation safety. This would allow greater recognition of deficiencies in airport safety and would present a united front for their correction to both private and governmental interests.

On the international level, the California Aviation Safety Council has already established through its members, excellent liaison and exchange of knowledge on mutual safety and airport disaster medical care planning with South Adelaide (Australia), the airports of Paris, Athens Airport and Zurich International Airport.

Current Interests

The council has a decided interest in a number of subjects involving aviation safety and is exploring them in depth with presentations by specialists. The following is a list of these subjects.

1. Toxicity problems of spray materials used by crop dusting pilots.
2. The proper containerization, labeling and designation of appropriate neutralizing procedures for dangerous chemicals shipped by air.
3. The use of fire-resistant and nontoxic material for cabin decor and insulation.
4. Research in the field to establish more effective means of passenger cabin evacuation in event of crash landing on land or sea.
5. Instruction in advanced first aid training for cabin attendants and annual certification.
6. Revision and improvement of basic first aid equipment aboard carrier aircraft.
7. Inclusion of annual test exercises for demonstration of the adequacy of airport disaster planning as one of the requirements of airport certification by the Federal Aviation Administration.

Refer to: Miller TA, Haftel AJ: Iatrogenic digital ischemia (Medical Information). West J Med 122:183-184, Feb 1975

Medical Information

Iatrogenic Digital Ischemia

TIMOTHY A. MILLER, MD
ANTHONY J. HAFTEL, MD
La Jolla

Figure 1.—Case 1. Appearance of fourth finger of left hand three days following dressing using Surgifix applied with a twist.

During a recent one-week period, four patients were seen in the emergency room for ischemic or gangrenous fingers secondary to circumferential constriction with a new dressing material. All had had finger wounds dressed in the same manner and with the same material. Although the method used was the same employed without complication for many years, Surgifix* had been substituted for an older dressing material (Tubgauze†). It is the purpose of this communication to alert the medical community to the potential danger of the new dressing material when it is *improperly* used.

Reports of Cases

Case 1.—A 5½-year-old boy sustained a minor laceration to the distal fourth finger of the left hand. Sutures were not required. A number 1 Surgifix bandage was applied in a layered fashion, with a twist at the proximal aspect of the phalanx. The next day the child complained of increasing pain that continued until he was brought back to the emergency room on the third day. The fourth finger was black with multiple bullae, and a sharp line of demarcation between gangrenous and viable tissue was present around the base of the proximal phalanx (Figure 1). The finger was completely anesthetic distal to this line, and only the slightest motion at the distal interphalangeal and proximal interphalangeal joints was present.

The patient was admitted to hospital and treated with antibiotics, plaster cast immobilization and elevation. After several surgical procedures during the succeeding four months, it became obvious that any degree of function of the finger would be minimal. The entire fourth finger and metacarpal eventually were amputated.

Case 2.—A 2-year-old girl was seen for an erythematous, painful left middle finger first noted two days before presentation. No cause could be ascertained. The patient was treated with benzathine penicillin G (Bicillin®) administered intramuscularly, and the finger was dressed with Surgifix. When the patient was seen the next day and the bandage released, the finger was found to be deeply cyanotic, again with a distinct line of demarcation around the base under the twist of the bandage.

Rapid improvement with resolution of infection followed minimal surgical debridement, elevation and immobilization. The patient was discharged on the eighth hospital day, with complete return to normal function.

Case 3.—A 25-year-old woman was treated for a laceration to the right thumb sustained on a broken soda bottle. The wound was sutured, and a circumferential multilayered Surgifix bandage was applied.

Two days later, the patient reported increasing pain in the thumb. On removal of the Surgifix bandage, the thumb was found to be blackened, cold and anesthetic. A clear line of demarcation was noted on the proximal phalanx. The patient was treated with antibiotics, immobilization and

*Surgifix—Manufactured and patented by F.R.A. s.n.c., Cisterna d'Asti (Italy) distributed in the USA by: Surgifix Hospital Products, Inc., 1154 E. Putnam Avenue, Greenwich, Connecticut.

†Tubgauze—School Manufacturing Company, Chicago, Illinois.

From the Department of Surgery, University of California, San Diego, School of Medicine, La Jolla.

Reprint requests to: T. A. Miller, MD, Division of Plastic Surgery, University of California, Los Angeles School of Medicine, Los Angeles, CA 90024.

Figure 2.—Example of correct use of Surgifix bandage.

elevation. The hospital course was uncomplicated, and complete restoration of sensation and function was achieved.

CASE 4.—A 24-year-old woman had a minor laceration of the right index finger dressed with Surgifix. On the following day, she reported pain and swelling. The constrictive bandage was removed, and a well-defined ring of constriction was noted at the base of the proximal phalanx. The pain and swelling were ameliorated, and admission to hospital was not necessary.

Discussion

Tubgauze is a fine mesh, slightly elastic gauze fashioned in graded cylindrical form and applied to affected digits and extremities with a metal "mandrel." The mandrel generally is twisted at the proximal aspect of the digit with each successive layer of application to help secure the dressing material and to create a firm but not constrictive bandage. Surgifix, on the other hand, is a considerably more elastic and coarser meshed net material fashioned in tubular form. We have used it effectively as a layer covering to maintain underlying gauze bandage (Figure 2) and in the management of large surface wounds such as burns.

The similar appearance of the two dressing materials makes it tempting to apply them in a like manner. Unfortunately, the experience reported here suggests that Surgifix, when twisted in a *multilayered* dressing on a digit, becomes a constrictive tourniquet. In each of the cases presented, a distinct line of demarcation between normal and ischemic tissue was evident immediately beneath the area at the base of the proximal digit.

It is not the purpose of this paper to condemn the use of Surgifix dressing material. On the contrary, it is an excellent innovation and an addition to the surgeon's armamentarium. We feel obligated, however, to alert the medical community to the potential dangers of this relatively new material when applied as described in this paper.

Refer to: Shimkin MB: BCG and cancer prevention (Medical Information). West J Med 122:185, Feb 1975

Medical Information

BCG and Cancer Prevention

MICHAEL B. SHIMKIN, MD, *La Jolla*

As long ago as 1929, Raymond Pearl[1] concluded that there was an antagonism between cancer and tuberculosis. Wilson and Maher,[2] in a sophisticated statistical reanalysis, not only could not substantiate such an antagonism but found a slight degree of positive association between the two diseases.

In more recent times, immunology has become an important, fertile field in cancer research. Tumor antigens, some related to oncogenic viruses and others as manifestations of dedifferentiation of neoplasms toward the embryonic state, appear full of promise for the future.[3] Burnet[4] contributed the concept of "immunologic surveillance" of the host over mutated, potential cancer cells that may arise from the somatic cells of the body. The development and growth of many experimental cancers in animals were shown to be influenced by immunologic mechanisms, such as stimulation by non-specific agents (for example, bacille Calmette Guérin [BCG] vaccination) and inhibition by pharmacologic and surgical procedures (for example, thymectomy).

Immune mechanisms are involved also in the genesis of at least certain types of human cancer. Perhaps the most convincing data show the high frequency of mesenchymal neoplasms among patients receiving organ transplants and maintained on immunosuppressive agents.[5]

In 1970, Davignon et al[6] published a note from Quebec indicating that leukemia mortality was less among BCG-vaccinated children than among a retrospectively gathered group of non-vaccinated children. Among 407,900 vaccinated children there were 96 deaths from leukemia; among 341,860 non-vaccinated children, there were 191 leukemic deaths, or over three times the frequency. Rosenthal et al[7] in 1972 reported a similar retrospective study in Chicago. There was one death from leukemia in 54,414 children vaccinated with BCG, and 21 leukemic deaths among 172,986 non-vaccinated children, a six-fold difference. However, a 21-year study of 64,126 persons in Georgia and Alabama reported by Comstock et al[8] gave no indication that BCG vaccination had either prevented or encouraged the development of leukemia, Hodgkin's disease or lymphosarcoma.

Serious criticisms and reservations regarding the biometric methodology used in the Chicago study have been recorded by Schneiderman and Levin.[9] Rosenthal et al[7] also realized the need for a prospectively-designed field trial to conclude that there was a protective role of BCG in childhood leukemia.

Nevertheless, the incomplete, albeit provocative, information has been extrapolated by some clinicians to support using BCG vaccination for the prevention of cancer. In one instance, an internist suggested BCG vaccination to an addicted, heavy cigarette smoker as an alternative to reducing the use of cigarettes.

Although quality controls have eliminated the tragic mistakes which complicated early use of the vaccine, complications still occur,[10] including granulomatus hepatitis which happened in 3 of 25 patients given BCG as immunotherapy for cancer.

BCG is a live, attenuated vaccine against tuberculosis. Its use on a wide scale even against tuberculosis in communities where tuberculosis has a low prevalence is not advocated.[11] As a cancer preventive, its use at this time on the basis of presently available knowledge is highly empirical, and thoroughly unjustified. Even without possible untoward effects of the procedure itself, subsequent exposure to tuberculosis would be masked, and the patient and the physician possibly lulled into a false sense of security.

These comments do not apply, of course, to designed clinical investigations to establish the possible value of immunotherapeutic measures in cancer.

From the Department of Community Medicine, University of California, San Diego, School of Medicine, La Jolla, CA 92037.

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in memoriam

Askey, Edwin Vincent, Los Angeles. Died December 11, 1974 in San Diego, aged 79. Graduate of the University of Pennsylvania, School of Medicine, Philadelphia, 1921. Licensed in California in 1923. Dr. Askey was a past president of the American Medical Association, of the California Medical Association, and of the Los Angeles County Medical Association, and a member of the Los Angeles County Medical Association.

Boyd, Winton Ray, Long Beach. Died November 13, 1974 in Long Beach of leukemia, aged 51. Graduate of the Creighton University School of Medicine, Omaha, 1947. Licensed in California in 1966. Dr. Boyd was a member of the Los Angeles County Medical Association.

Brakensiek, Clifton Mack, Bellflower. Died December 2, 1974, aged 65. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1940. Licensed in California in 1940. Dr. Brakensiek was a member of the Los Angeles County Medical Association.

Galton, Richard S., El Sobrante. Died December 13, 1974 in El Sobrante, aged 54. Graduate of the University of California Medical School, Berkeley-San Francisco, 1945. Licensed in California in 1945. Dr. Galton was a member of the Alameda-Contra Costa Medical Association.

Gee, Vernon R., Redding. Died December 23, 1974 in Redding of heart disease, aged 54. Graduate of Northwestern University Medical School, Chicago, 1947. Licensed in California in 1956. Dr. Gee was a past president and a member of the Shasta-Trinity County Medical Society.

Harding, Nancy Jane, La Crescenta. Died November 15, 1974 in Glendale of cancer, aged 60. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1935. Licensed in California in 1935. M.D. degree from California College of Medicine, 1962. Dr. Harding was an associate member of the Los Angeles County Medical Association.

Hardre, Rene, Sacramento. Died October 6, 1974 in Sacramento of heart disease, aged 61. Graduate of Rush Medical School, Chicago, 1939. Licensed in California in 1958. Dr. Hardre was a member of the Sacramento County Medical Association.

MacDonald, James Lindell, Oakland. Died November 6, 1974 in Walnut Creek of heart disease, aged 65. Graduate of the University of Southern California School of Medicine, Los Angeles, 1939. Licensed in California in 1939. Dr. MacDonald was a retired member of the Alameda-Contra Costa Medical Association.

MacPherson, Fraser Lapp, San Diego. Died December 17, 1974 in San Diego, aged 78. Graduate of the University of California Medical School, Berkeley-San Francisco, 1922. Licensed in California in 1922. Dr. MacPherson was a retired member of the San Diego County Medical Society.

Muir, James C., sr., San Jose. Died November 28, 1974 in San Jose of cancer, aged 70. Graduate of Northwestern University Medical School, Chicago, 1931. Licensed in California in 1935. Dr. Muir was a retired member of the Santa Clara County Medical Society.

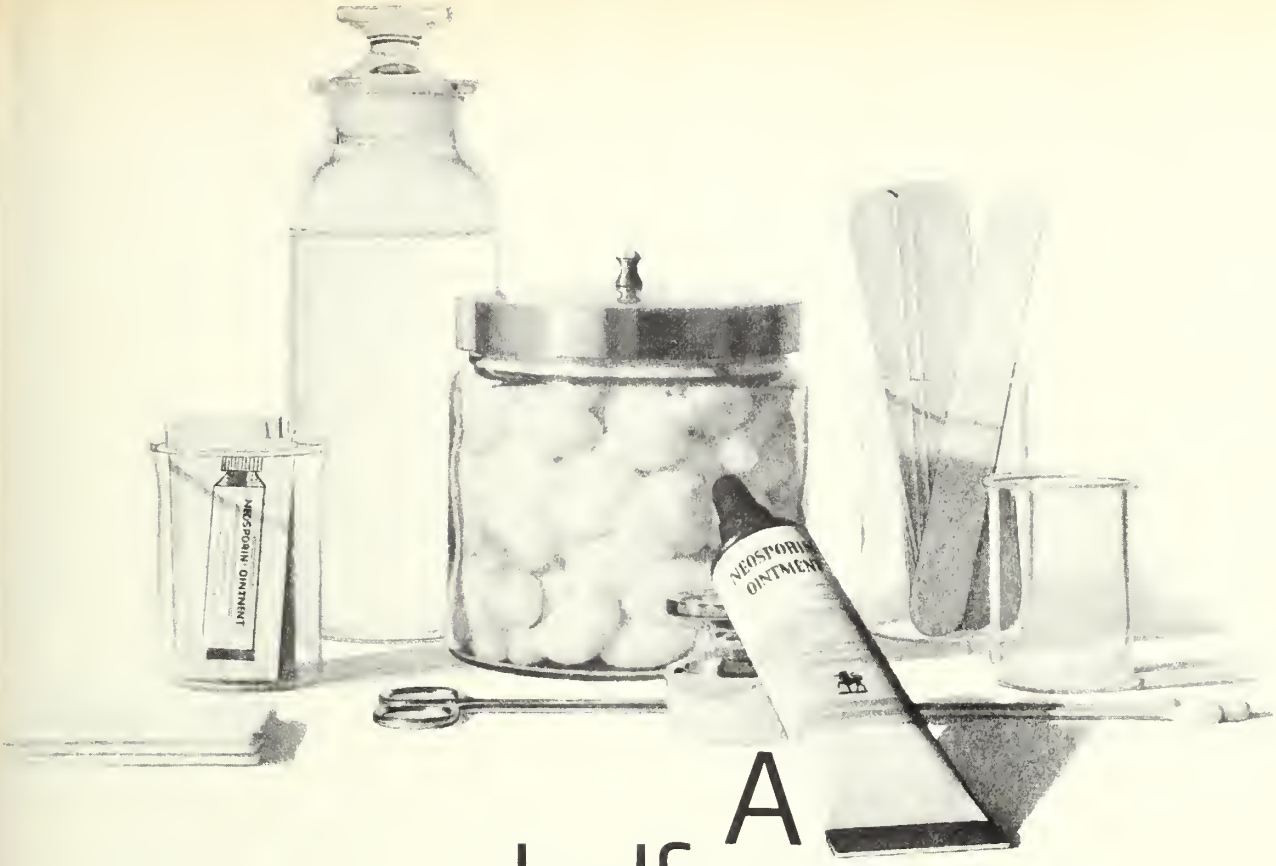
O'Connell, Noreen Mary, Fresno. Died December 8, 1974, aged 45. Graduate of Georgetown University School of Medicine, Washington, DC, 1955. Licensed in California in 1970. Dr. O'Connell was a member of the Fresno County Medical Society.

Ranker, Emery Romain, jr., Oakland. Died December 17, 1974 in Oakland, aged 46. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1954. Licensed in California in 1954. Dr. Ranker was a member of the Alameda-Contra Costa Medical Association.

Regello, Irene M., Oakland. Died December 3, 1974 in San Francisco of leukemia, aged 52. Graduate of University of California Medical School, Berkeley-San Francisco, 1952. Licensed in California in 1953. Dr. Regello was an associate member of the Alameda-Contra Costa Medical Association.

Rhone, Thomas Beck, Orange. Died December 2, 1974, aged 71. Graduate of the University of Colorado School of Medicine, Denver, 1927. Licensed in California in 1934. Dr. Rhone was a retired member of the Orange County Medical Association.

Smith, Richard Paul, Hayward. Died December 11, 1974 in San Leandro, aged 44. Graduate of the University of Buffalo School of Medicine, 1956. Licensed in California in 1962. Dr. Smith was a member of the Alameda-Contra Costa Medical Association.



A half-ounce of prevention

Use it to prevent a topical infection. Or to treat one that's already started. In either case, it's good medicine. Whether for lacerations, burns, open wounds, IV catheter or surgical aftercare. Neosporin® Ointment provides broad antibacterial coverage against common susceptible pathogens. And since it contains three antibiotics that are rarely used systemically, the risk of sensitization is reduced. Neosporin Ointment. A half-ounce of prevention. Also available in a full ounce of prevention and in convenient foil packets.

Neosporin Ointment carried on Apollo and Skylab missions.

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Each gram contains: Aerosporin® brand Polymyxin B Sulfate 5,000 units; zinc bacitracin 400 units; neomycin sulfate 5 mg (equivalent to 3.5 mg neomycin base); special white petrolatum qs.
In tubes of 1 oz and 1/2 oz and 1/32 oz (approx.) foil packets.

INDICATIONS: *Therapeutically,* used as an adjunct to appropriate systemic therapy for topical infections, primary or secondary, due to susceptible organisms, as in: • infected burns, skin grafts, surgical incisions, otitis externa • primary pyodermas (impetigo, ecthyma, sycosis vulgaris, paronychia) • secondarily infected dermatoses (eczema, herpes, and seborrheic dermatitis) • traumatic lesions, inflamed or suppurating as a result of bacterial infection.
Prophylactically, the ointment may be used to prevent bacterial contamination in burns, skin grafts, incisions, and other clean lesions. For abrasions, minor cuts and wounds accidentally incurred, its use may prevent the development of infection and permit wound healing.

CONTRAINDICATIONS: Not for use in the eyes or external ear canal if the eardrum is perforated. This product is contraindicated in those individuals who have shown hypersensitivity to any of the components.

WARNING: Because of the potential hazard of nephrotoxicity and ototoxicity due to neomycin, care should be exercised when using this product in treating extensive burns, trophic ulceration and other extensive conditions where absorption of neomycin is possible. In burns where more than 20 percent of the body surface is affected, especially if the patient has impaired renal function or is receiving other aminoglycoside antibiotics concurrently, not more than one application a day is recommended.

PRECAUTIONS: As with other antibacterial preparations, prolonged use may result in overgrowth of nonsusceptible organisms, including fungi. Appropriate measures should be taken if this occurs.

ADVERSE REACTIONS: Neomycin is a not uncommon cutaneous sensitizer. Articles in the current literature indicate an increase in the prevalence of persons allergic to neomycin. Ototoxicity and nephrotoxicity have been reported (see Warning section).

Complete literature available on request from Professional Services Dept. PML.

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IN GONORRHEA

INJECTION

Wycillin®

(STERILE PROCAINE PENICILLIN G SUSPENSION) WYETH

Gonorrhea, according to the national Center for Disease Control, is, if the parenteral route is chosen, most effectively treated with aqueous procaine penicillin G. In uncomplicated cases, administration of 4.8 million units together with 1 gram oral probenecid, given at least 30 minutes prior to injection, is recommended.

Indications: In treatment of moderately severe infections due to penicillin G-sensitive microorganisms sensitive to the low and persistent serum levels common to this particular dosage form. Therapy should be guided by bacteriological studies (including sensitivity tests) and by clinical response.

NOTE: When high sustained serum levels are required use aqueous penicillin G, IM or IV.

The following infection will usually respond to adequate dosages of intramuscular procaine penicillin G.—*N. gonorrhoeae:* acute and chronic (without bacteremia).

For deep intramuscular injection only.

Contraindications: Previous hypersensitivity reaction to any penicillin.

Warnings: Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy.

Serious anaphylactoid reactions require immediate emergency treatment with epinephrine. Oxygen and intravenous corticosteroids should also be administered as indicated.

Although anaphylaxis is more frequent following parenteral therapy it has occurred in patients on oral penicillins. These reactions are more apt to occur in individuals with a history of sensitivity to multiple allergens.

There have been well documented reports of individuals with a history of penicillin hypersensitivity reactions who have experienced severe hypersensitivity reactions when treated with a cephalosporin. Before therapy with a penicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, and other allergens. If an allergic reaction occurs, the drug should be discontinued and the patient treated with the usual agents e.g., pressor amines, antihistamines and corticosteroids.

Precautions: Use cautiously in individuals with histories of significant allergies and/or asthma.

Carefully avoid intravenous or intraarterial use, or injection into or near major peripheral nerves or blood vessels, since such injections may produce neurovascular damage.

A small percentage of patients are sensitive to procaine. If there is a history of sensitivity, make the usual test: Inject intradermally 0.1 cc. of a 1 to 2 percent procaine solution. Development of an erythema, wheal, flare or eruption indicates procaine sensitivity. Sensitivity should be treated by the usual methods, including barbiturates, and procaine penicillin preparatio should not be used. Antihistaminics appear beneficial in tre ment of procaine reaction.

The use of antibiotics may result in overgrowth of nonsu ceptible organisms. Constant observation of the patient is ess tial. If new infections due to bacteria or fungi appear duri therapy, discontinue penicillin and take appropriate measure

If allergic reaction occurs, withdraw penicillin unless, in t opinion of the physician, the condition being treated is l threatening and amenable only to penicillin therapy.

When treating gonococcal infections with suspected prima or secondary syphilis, perform proper diagnostic procedur including darkfield examinations. In all cases in which concor tant syphilis is suspected, perform monthly serological tests for least four months.

Adverse Reactions: (Penicillin has significant index of se sitization) skin rashes, ranging from maculopapular eruptions exfoliative dermatitis; urticaria; serum sickness-like reactio including chills, fever, edema, arthralgia and prostration. Seve and often fatal anaphylaxis has been reported. (See "Warnings."

As with other antisyphilitics, Jarisch-Herxheimer reaction h been reported.

Administration and Dosage: Administer only by *deep int muscular injection,* in upper outer quadrant of buttock. In infa and small children, midlateral aspect of thigh may be preferab When doses are repeated, vary injection site. Before injecti aspirate to be sure needle bevel is not in blood vessel. If blo appears, remove needle and inject in another site.

Although some isolates of *Neisseria gonorrhoeae* have c creased susceptibility to penicillin, this resistance is relative, n absolute, and penicillin in large doses remains the drug of choi Physicians are cautioned not to use less than recommend doses.

Gonorrheal infections (uncomplicated)—Men or Women: million units intramuscularly divided into at least two doses a injected at different sites at one visit, together with 1 gram of c probenecid, preferably given at least 30 minutes prior to injectio

NOTE: Treatment of severe complications of gonorrhea shou be individualized using large amounts of short-acting penicil Gonorrheal endocarditis should be treated intensively w aqueous penicillin G. Prophylactic or epidemiologic treatment gonorrhea (male and female) is accomplished with same tre ment schedules as for uncomplicated gonorrhea.

Retreatment: The National Center for Disease Control, Ve real Disease Branch, U.S. Dept. H.E.W. recommends:

Test cure procedures at approximately 7-14 days after thera In the male, a gram-stained smear is adequate if positive; oth wise, a culture specimen should be obtained from the ante urethra. In the female, culture specimens should be obtain from both the endocervical and anal canal sites.

Retreatment in males is indicated if urethral discharge pers 3 or more days following initial therapy and smear or cult remains positive. Follow-up treatment consists of 4.8 million un I.M. divided in 2 injection sites at single visit.

In uncomplicated gonorrhea in the female, retreatment indicated if follow-up cervical or rectal cultures remain positive *N. gonorrhoeae.* Follow-up treatment consists of 4.8 million un daily on 2 successive days.

Syphilis: all gonorrhea patients should have a serologic test syphilis at the time of diagnosis. Patients with gonorrhea w also have syphilis should be given additional treatment app priate to the stage of syphilis.

Composition: Each disposable syringe 2,400,000 units (4 size) contains procaine penicillin G in a stabilized aqueous s pension with sodium citrate buffer, and as w/v approximately 0. lecithin, 0.5% carboxymethylcellulose, 0.5% povidone, 0.1% mett paraben, and 0.01% propylparaben. The multiple-dose 10-cc. contains per cc. 300,000 units procaine penicillin G in a stabiliz aqueous suspension with sodium citrate buffer and approximat 7 mg. lecithin, 2 mg. carboxymethylcellulose, 3 mg. povid 0.5 mg. sorbitan monopalmitate, 0.5 mg. polyoxyethylene sorb monopalmitate, 1.2 mg. methylparaben, and 0.14 mg. pro paraben.

Five are graduating with honors. How many with VD?

On the average, you can figure the incidence of VD among teenagers at about 900 per 100,000 population.* And growing.

Among those in the 20-24 age-group, the incidence is even higher. And it, too, is growing.

In the long run, a populace educated to the risks and prevention of VD is probably the best answer to the problem. Meanwhile, though, adequate doses of the recommended types of penicillin remain a formidable weapon.

IN SYPHILIS

INJECTION

Bicillin® LONG-ACTING

(STERILE BENZATHINE PENICILLIN G SUSPENSION) WYETH

Syphilis is preferably treated with benzathine penicillin G, which is also the drug of choice for prophylaxis after exposure. Administration of 2.4 million units (1.2 million in each buttock) usually cures most cases of primary, secondary and latent syphilis with negative spinal fluid.

Indications: In treatment of infections due to penicillin G-sensitive microorganisms that are susceptible to the low and very prolonged serum levels common to this particular dosage form. Therapy should be guided by bacteriological studies (including sensitivity tests) and by clinical response.

The following infections will usually respond to adequate dosage of intramuscular benzathine penicillin G.—Venereal infections: Syphilis, yaws, bejel and pinta.

For deep intramuscular injection only.

Contraindications: Previous hypersensitivity reaction to any penicillin.

Warnings: Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported. Anaphylaxis is more frequent following parenteral therapy but has occurred with oral penicillins. These reactions are more apt to occur in individuals with history of sensitivity to multiple allergens.

Severe hypersensitivity reactions with cephalosporins have been well documented in patients with history of penicillin hypersensitivity. Before penicillin therapy, carefully inquire into previous hypersensitivity to penicillins, cephalosporins and other allergens. If allergic reaction occurs, discontinue drug and treat with usual agents, e.g., pressor amines, antihistamines and corticosteroids.

Precautions: Use cautiously in individuals with histories of significant allergies and/or asthma.

Carefully avoid intravenous or intraarterial use, or injection into or near major peripheral nerves or blood vessels, since such injection may produce neurovascular damage.

In streptococcal infections, therapy must be sufficient to eliminate the organism; otherwise the sequelae of streptococcal disease may occur. Take cultures following completion of treatment to determine whether streptococci have been eradicated.

Prolonged use of antibiotics may promote overgrowth of nonsusceptible organisms including fungi. Take appropriate measures should superinfection occur.

Adverse Reactions: Hypersensitivity reactions reported are skin eruptions (maculopapular to exfoliative dermatitis), urticaria and other serum sickness reactions, laryngeal edema and anaphylaxis. Fever and eosinophilia may frequently be only reaction observed. Hemolytic anemia, leucopenia, thrombocytopenia, neuropathy and nephropathy are infrequent and usually associated with high doses of parenteral penicillin.

As with other antisyphilitics, Jarisch-Herxheimer reaction has been reported.

Administration and Dosage: Venereal infections—

Syphilis—Primary, secondary and latent—2.4 million units (1 dose).

Late (tertiary and neurosyphilis)—2.4 million units at 7 day intervals for three doses.

Congenital—under 2 years of age, 50,000 units/Kg. body weight; ages 2-12 years, adjust dosage based on adult dosage schedule.

(Shake multiple-dose vial vigorously before withdrawing the desired dose.) Administer by **deep intramuscular injection** in the upper outer quadrant of the buttock. In infants and small children, the midlateral aspect of the thigh may be preferable. When doses are repeated, vary the injection site. Before injecting the dose, aspirate to be sure needle bevel is not in a blood vessel. If blood appears, remove the needle and inject in another site.

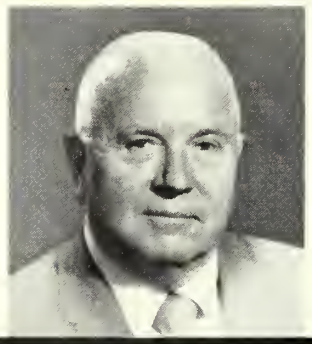
Composition: Units benzathine penicillin G (as active ingredient): 2,400,000 units in 4-cc. single dose disposable syringe. Each disposable syringe also contains in aqueous suspension with sodium citrate buffer, as w/v approximately 0.5% lecithin, 0.6% carboxymethylcellulose, 0.6% povidone, 0.1% methylparaben, and 0.01% propylparaben. 300,000 units per cc.—10-cc. multi-dose vial. Each cc. also contains sodium citrate buffer, approximately 6 mg. lecithin, 3 mg. povidone, 1 mg. carboxymethylcellulose, 0.5 mg. sorbitan monopalmitate, 0.5 mg. polyoxyethylene sorbitan monopalmitate, 1.2 mg. methylparaben, and 0.14 mg. propylparaben.

Wyeth Laboratories
Philadelphia, Pa. 19101

*U.S. Dept. of Health, Education, and Welfare: VD Fact Sheet 1972. Publication No. (HSM) 73-8195.

The Role of the Detail Man

Opinion & Dialogue

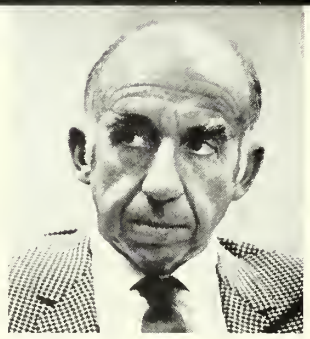


Dr. Willard Gobbell
Family Physician
Encino, California

"I may be prejudiced, but I am very much in favor of the detail men I meet. Most of them are knowledgeable about the drugs they promote and can be a great help in acquainting me with new medication."

Family Physician's Perception

I think that most general practitioners in this area feel as I do about the detail man. Over the years I have gotten to know most of the men who visit me regularly and they in turn have become aware of my particular interests and the nature of my practice. They, therefore, limit their discussion as much as possible to the areas of interest to me. Since I usually see the same representative again in future visits, it is in his best interest to supply me with the most honest, factual, as well as up-to-date information about his products.



Dr. Jeremiah Stamler
Chairman
Department of Community Health and Preventive Medicine, and Dingman Professor of Cardiology
Northwestern University Medical School

"In the total picture of dealing with health problems in this country, there is a potential for detail men to play a meaningful role."

The Positive Influence

My contact with representatives and salesmen of the pharmaceutical industry is the type of contact that people in a medical center, research people, and academic people have and that's in all likelihoo on a somewhat different level from that of the practicing physician.

Let me touch on how I personally perceive the role of the sales representative. These men reach large numbers of health professionals. Thus they could be—and at times actually are—disseminators of useful information. They could consistently serve a real educational function in their ability to discuss their products.

At present they do distribute printed material, brochures and pamphlets—some of it scientifically sound and therefore truly useful—as well as some excellent films produced by the pharmaceutical industry. When they function in this

Is He a Source of Information?

Yes, with certain reservations. The average sales representative has a great fund of information about the drug products he is responsible for. He is usually able to answer most questions fully and intelligently. He can also supply reprints of articles that contain a great deal of information. Here, too, I exercise some caution. I usually accept most of the statements and opinions that I find in the papers and studies which come from the larger teaching facilities. It goes without saying that a physician should also rely on other sources for his information on pharmacology.

Training of Sales Representatives

Ideally, a candidate for the position as a sales representative of a pharmaceutical company should be a graduate pharmacist who has a questioning mind. I don't think this is possible in every case, and so it becomes the responsibility of the pharmaceutical company to train these individuals comprehensively. It is of very great importance that the detail man's knowledge of the product he represents be constantly reviewed as well as updated. This phase of the sales representative's education should be a major responsibility of the medical department of the pharmaceutical company.

I am certain that most of these companies take special care to give their detail men a great deal of information about the products they produce—information about indications, contraindications, side effects and precautions. Yet, although most of the detail men are well informed, some, unfortunately, are not. It might be helpful if sales representatives were reassessed every few years to determine whether or not they are able to fulfill their important function. Incidentally, I feel the same way about periodic assessments of everyone in the health care field, whether they be general practitioners, surgeons or salesmen.

Value of Sampling

I personally am in favor of limited sampling. I do not use sampling in order to perform clinical testing of a drug. I feel that drug testing should rightly be left to the pharmacology researcher and to the large teaching institutions where such testing can be done in a controlled environment.

I do not use samples as a "starter dose" for my patients. I do, however, find samples of drugs to be of value in that they permit me to see what the particular medication looks like. I get to see the various forms of the particular medication at first hand, and if it is in a liquid form I take the time to taste it. In that way I am able to give my patients more complete information about the particular medications that I prescribe for them.

capacity they are indeed useful; particularly in the fact that they disseminate broadly based educational material and serve not just as "pushers" of their drugs.

The Other Side of the Coin

Obviously, the pharmaceutical companies are not producing all this material as a labor of love—they are in the business of selling products for profit. In this regard the ambitious and improperly motivated sales representative can exert a negative influence on the practicing physician, both by presenting a one-sided picture of his product, and by encouraging the practitioner to depend too heavily on drugs for his total therapy. In these ways, the salesman has often distorted objective reality and undermined his potential role as an educator.

The Industry Responsibility

Since the detail man must be an information resource as well as a representative of his particular pharmaceutical company, he should be carefully selected and thoroughly trained. That training, perforce, must be an ongoing one. There must be a continuing battle within and with the pharmaceutical industry for high quality not only in the selection and training of its sales representatives, but also in the development of all of its promotional and educational material.

The industry must be ready to accept constructive as well as corrective criticism from experts in the field and consumer spokesmen, and be willing to accept independent peer review. The better educated and prepared the salesman is, the more medically accurate his materials, the better off the pharmaceutical industry, health professionals and the public—*i.e.*, the patients—will be.

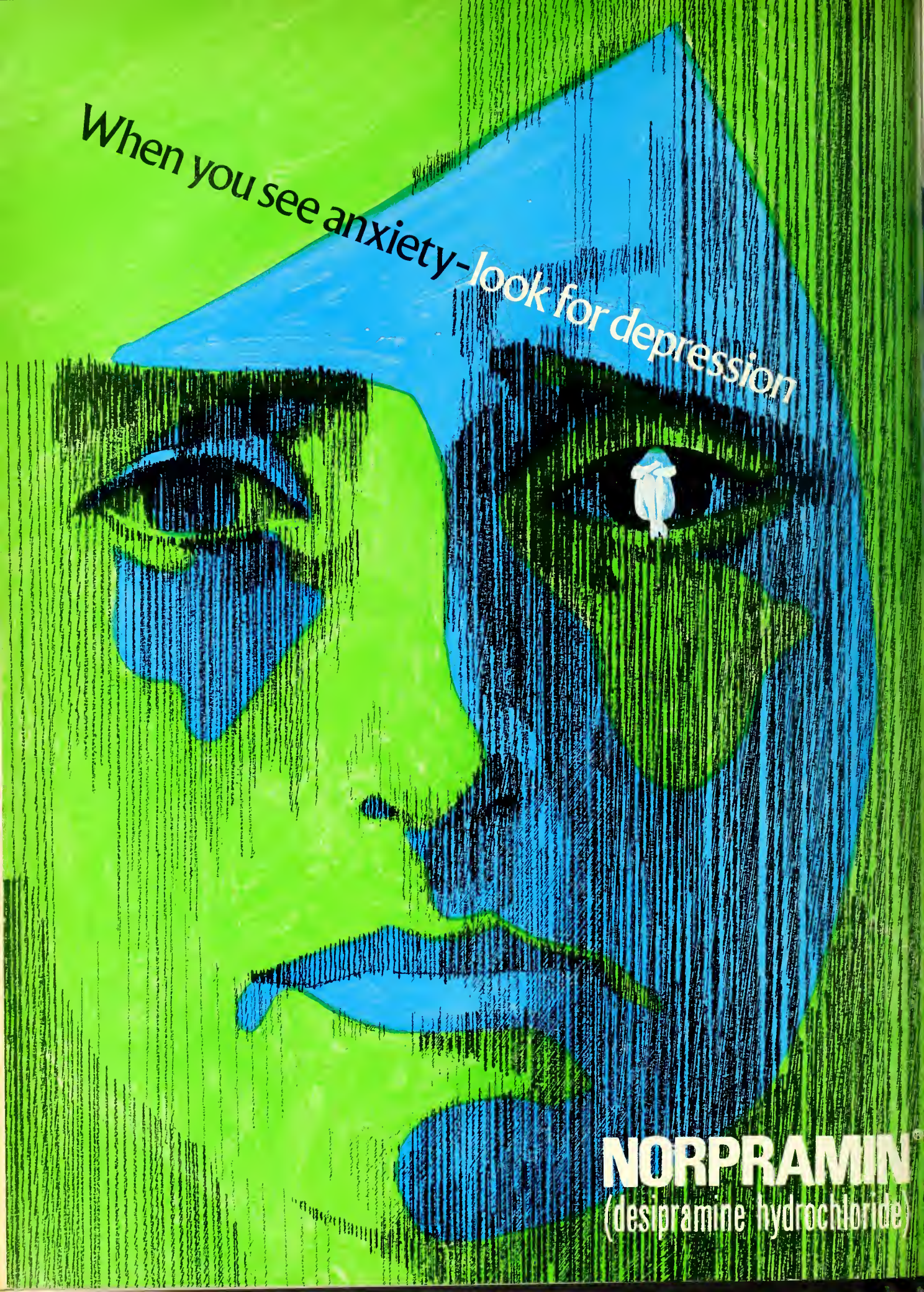
Physician Responsibility

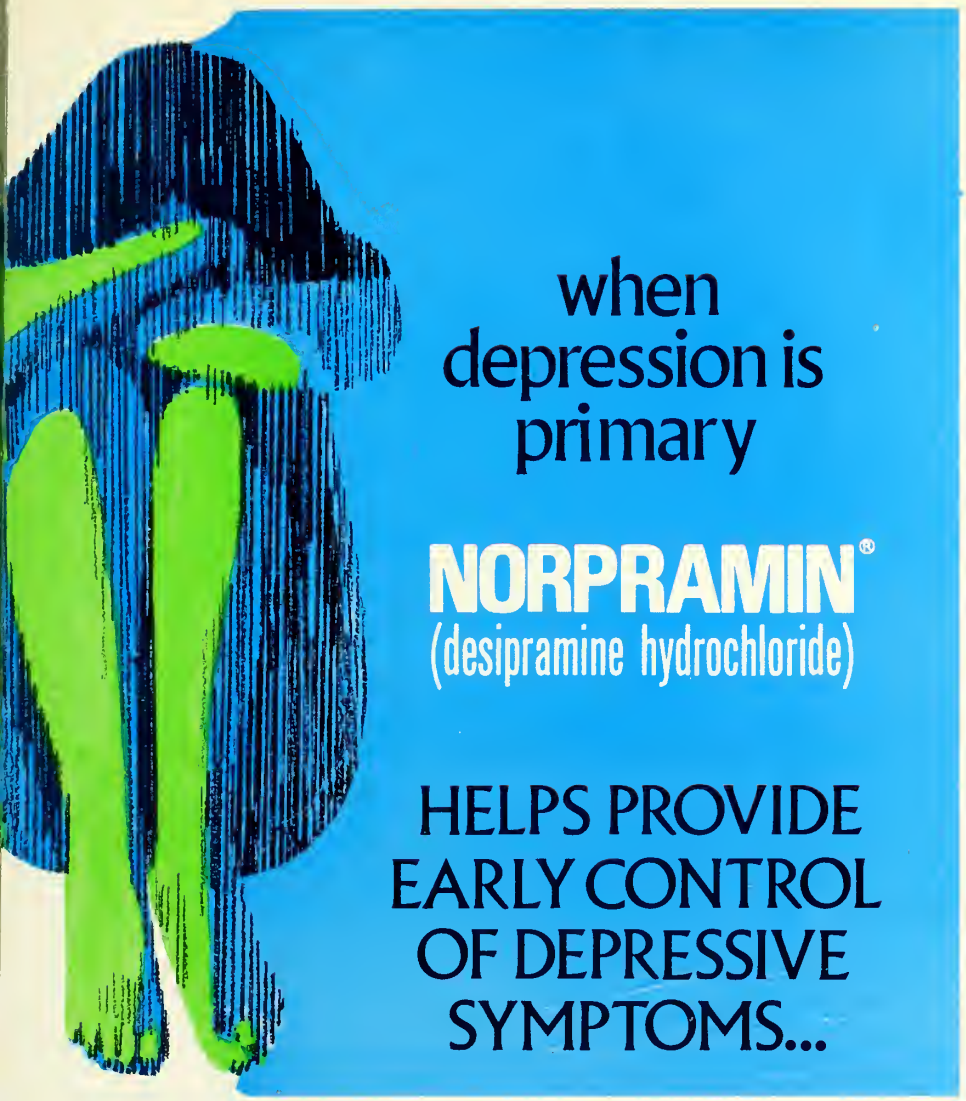
The practicing physician is in constant need of up-dated information on therapeutics, including drugs. He should and does make use of drug information and answers to specific questions supplied by the pharmaceutical representative. However, that information must not be his main source of continuing education. The practitioner must keep up with what is current by making use of scientific journals, refresher courses, and information received at scientific meetings.

The practicing physician not only has the right, but has the responsibility to demand that the pharmaceutical company and its representatives supply a high level of valid and useful information. I feel certain that if such a high level is demanded by the physician as well as the public, this demand will be met by an alert and concerned pharmaceutical industry.

From my experience, my impression is that sectors of the pharmaceutical industry are indeed ethical. I challenge the industry as a whole to live up to that word in its finest sense.

Pharmaceutical Manufacturers Association
1155 Fifteenth Street, N.W.
Washington, D.C. 20005


When you see anxiety-look for depression
NORPRAMIN®
(desipramine hydrochloride)



Anxiety is an invidious symptom. It feeds upon sickness, gnaws, grows and invades every cranny of psychic pathology adding intensity to torment. Anxiety as a symptom secondary to depression may be so dominant that it obscures the primary diagnosis. It may suggest treatment with tranquilizers which often help. But as the vampire of legend had to have a laurel stake driven through its heart to truly die, so anxiety secondary to depression will not cease to nibble and bite until an antidepressant eradicates the primary illness—and symptomatic anxiety starves.

IN BRIEF:

Indications: Norpramin® (desipramine hydrochloride) is indicated for the relief of depressive symptoms. Endogenous depressions are more likely to be alleviated than others.

Contraindications: Desipramine hydrochloride should not be given within two weeks of treatment with a monoamine oxidase inhibitor. Contraindications include the acute recovery period following myocardial infarction and hypersensitivity to the drug. Cross sensitivity with other dibenzazepines is a possibility.

Warnings: 1. Extreme caution should be used in patients: (a) with cardiovascular disease, (b) with a history of urinary retention or glaucoma, (c) with thyroid disease or those on thyroid medication, (d) with a history of seizure disorder. 2. This drug is capable of blocking the antihypertensive effect of guanethidine and similarly acting compounds. 3. *Use in Pregnancy:* Safe use during pregnancy and lactation has not been established. 4. *Use in Children:* Norpramin® (desipramine hydrochloride) is not recommended for use in children. 5. This drug may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. Therefore, the patient should be cautioned accordingly.

Precautions: This drug should be dispensed in the least possible quantities to depressed outpatients, since suicide has been accomplished with drugs of this class. If possible, dispense in child-resistant containers. It should be kept out of reach of children. Reduce dosage, or alter treatment, if serious adverse effects occur. Norpramin® (desipramine hydrochloride) therapy in patients with manic-depressive illness may induce a hypomanic state after the depressive phase terminates and may cause exacerbation of phychosis in schizophrenic patients. Use cautiously with anticholinergic or sympathomimetic drugs. Response to alcoholic beverages may be exaggerated. In the concurrent administration of ECT and antidepressant drugs one should consider the possibility of increased risk relative to benefits. Discontinue as soon as possible prior to elective surgery because of possible cardiovascular effects. Hypertensive episodes have been observed during surgery in patients on desipramine hydrochloride. Leukocyte and differential counts should be performed in any patient who develops fever and sore throat during therapy; the drug should be discontinued if there is neutropenia.

Adverse Reactions: *Cardiovascular:* hypotension, hypertension, tachycardia, palpitation, arrhythmias, heart block, myocardial infarction, stroke. *Psychiatric:* confusional states (especially in the elderly), hallucinations, disorientation, delusions; anxiety, agitation; insomnia and nightmares; hypomania; exacerbation of phychosis. *Neurological:* paresthesias of extremities; incoordination, ataxia, tremors, peripheral neuropathy; extrapyramidal symptoms; seizures; alteration in EEG patterns; tinnitus. *Anticholinergic:* dry mouth, and rarely associated sublingual adenitis; blurred vision, disturbance of accommodation, mydriasis; constipation, paralytic ileus; urinary retention, delayed micturition, hypotonic bladder. *Allergic:* skin rash, petechiae, urticaria, itching, photosensitization, edema (of face and tongue or general), drug fever. *Hematologic:* agranulocytosis, eosinophilia, purpura, thrombocytopenia. *Gastrointestinal:* anorexia, nausea and vomiting, epigastric distress, peculiar taste, abdominal cramps, diarrhea, stomatitis, black tongue. *Endocrine:* gynecomastia; breast enlargement and galactorrhea in the female; increased or decreased libido, impotence, testicular swelling; elevation or depression of blood sugar levels. *Other:* jaundice (simulating obstructive), altered liver function; weight gain or loss; perspiration, flushing; urinary frequency, nocturia; parotid swelling; drowsiness, dizziness, weakness and fatigue, headache; alopecia. *Withdrawal Symptoms:* Though not indicative of addiction, abrupt cessation after prolonged therapy may produce nausea, headache and malaise.

Dosage and Administration: *The usual adult dose:* 50 mg. three times daily; increase if necessary after 7 to 10 days to maximum of 200 mg. daily. Dosages above 200 mg. per day are not recommended. *Maintenance:* At a lower dose adequate to maintain remission. *Adolescent and geriatric patient dose:* 25 to 50 mg. daily if necessary.

Overdosage: There is no specific antidote for desipramine, nor are there specific phenomena of diagnostic value characterizing poisoning by the drug. The principles of management of coma and shock by means of the mechanical respirator, cardiac pacemaker, monitoring of central venous pressure and regulation of fluid- and acid-base balance are well known in most medical centers. If heart failure is imminent, digitalize promptly.

Manufactured by LAKESIDE LABORATORIES
Division of Richardson-Merrell Inc

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LAKESIDE LABORATORIES, INC.
Milwaukee, Wisconsin 53201

(Continued from Page 13)

PHYSICIANS WANTED

HEALTH OFFICER—$31,789-$38,807. Santa Barbara County. To plan and direct Countywide public health and sanitation program. Cal. MD license, or eligibility to obtain, and 5 years experience in public health agency including 1 year in administrative capacity. Apply Personnel Dept., 123 E. Anapamu St., Santa Barbara, CA 93101 by February 14, 1975.

INTERNIST, Board Certified—Full or part time internist with interest in relaxed practice to include disability evaluations, compensation evaluations and some private practice. Terms negotiable. Reply: Redhill Medical Group, 18102 Irvine Blvd., Suite 202, Tustin, CA 92680.

ORTHOPEDIC SURGEON—Fulltime for multispecialty group practice. Salary with future partnership. Terms negotiable. Reply: Redhill Medical Group, 18102 Irvine Boulevard, Suite 202, Tustin, CA 92680.

FAMILY/GENERAL PRACTITIONERS: For expanding and innovative comprehensive health plan in Southern California area. Work with a full complement of multidisciplinary health professionals. Competitive salary with excellent fringe benefits. Send curriculum vitae to: Health Services Director, Northeast Valley Health Corporation, 14935 Rinaldi St., Suite 603, Mission Hills, CA 91345; (213) 365-0861.

PRACTICES FOR SALE

GENERAL PRACTICE—Very ective solo General Prectice; 23 years established in exclusive Encino; will introduce; terms negotiable. Fully furnished and equipped suite in large medical building with adequate private parking. Three open staff hospitals very close. Annual Gross $105,000. Call (213) 981-4778 or write Grobstein, Padolsky, Bridge & Goldman, 15233 Ventura Blvd., Suite 912, Sherman Oaks, CA 91403.

GYN practice immediately available in California (North Bay area) Box 9405, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

SITUATIONS WANTED

PATHOLOGIST—37 years, university trained, Board Certified AP-CP, excellent references, good experience, California licensed, wishes relocation in California. Apply Box 9401, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

PATHOLOGIST—Seeking director or associate position in California. Board certified in AP-CP. California license. Ten years experience as director of laboratory in small hospitals. Immediate availability. Phone (906) 786-0999. Write P.O. Drawer 100, Escanaba, Mich. 49829.

BOARD CERTIFIED SURGEON, FACS; Abdominal, GYN, and Hand Surgery. Desires So. California relocation. Send details of opening to Box 9406, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

OFFICES FOR LEASE OR RENT

FOR RENT: The newest and largest professionel building in the South San Diego community of Imperial Beach, will be completed in Jenuary 1975. Suites available can be customized to suit tenant. This is an excellent opportunity for pediatrics, gynecology, dermatology, ophthalmology, general surgery, generel practice, internal medicine and psychiatry. Photos and particulars available upon request from John E. Geis, DDS, 218 Palm Ave., Imperial Beech, CA 92032; office (714) 424-3931.

LEASE 1200 SQ. FT. SUITE. Four treatment rooms with or without equipment. G.P. leaving for health reasons; San Mateo area; (415) 341-8440.

INTERNISTS

Board Certified or eligible; Family Practitioners; for multi-specialty group on Island of Oahu. Also Pediatrician willing to do general practice for Island of Maui. Starting salary negotiable. Excellent fringe benefits. Write: Hawaii Permanente Medical Group, Inc., 1697 Ala Moana Blvd., Honolulu, Hawaii 96815.

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FULLERTON—Medical Suite for lease, in a 4-5 unit Medical-Dental building. We will build to suit your taste and you will be the only Medical Doctor in the surrounding neighborhood. John T. Liem, DDS, 3610 N. Harbor, Fullerton, CA 92635 or Call (714) 525-2381.

BEAUTIFUL SAN DIEGO—Efficient office ideal for 1 or 2 physicians near Mission Bay. Furnished and equipped for lab, x-ray, emergency, peds. Ground floor, A/C, parking. R. C. Mowry, MD, (714) 273-4285.

MEDICAL OFFICE-VACANT—Previous MD will help establish business w/old records etc. Building in Marin County, CA. 1450 Sq. Ft. w/room for 2-plus MD's. Some equipment for sale. Price $57,500 and owner may help in financing. **Marin Town & Country Reelty**, P.O. Box 154, San Rafael, CA 94902; (415) 454-3145; Eve (415) 456-5569.

BOOKS RECEIVED

Books received by THE WESTERN JOURNAL OF MEDICINE *are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.*

ADVANCES IN PRIMARY CARE—Conference Proceedings in Honolulu, Hawaii February 16-22, 1974—Edited by Marta C. Kallstrom and Stephen R. Yarnall, MD, President of Medical Computer Services Association, Seattle. Medical Computer Services Association, 1107 N.E. 45th Street, Seattle (98105), 1974. 195 pages, $16.00 (paperback).

ALPHAGENICS—How to Use Your Brain Waves to Improve Your Life—Anthony A. Zaffuto, PhD, with Mary Q. Zaffuto. Doubleday & Company, Inc., 245 Park Avenue, New York City (10017), 1974. 245 pages, $6.95.

ANTICIPATORY GRIEF—Edited by Bernard Schoenberg, MD, Arthur C. Carr, PhD, Austin H. Kutscher, DDS, David Peretz, MD, and Ivan K. Goldberg, MD. Columbia University Press, 562 West 113th Street, New York City (10025), 1974. 381 pages, $12.50.

CONTROVERSY IN OBSTETRICS AND GYNECOLOGY II—Edited by Duncan E. Reid, MD, Late Clinical Professor of Obstetrics and Gynecology, University of Arizona College of Medicine; and C. D. Christian, MD, Professor and Head of the Department of Obstetrics and Gynecology, University of Arizona College of Medicine. W. B. Saunders Company, West Washington Square, Philadelphia (19105), 1974. 854 pages, with 133 illustrations, $28.50.

THE DICTIONARY OF CALORIES AND CARBOHYDRATES—A new and revised version of CALORIES AND CARBOHYDRATES—Barbara Kraus. Grosset & Dunlap Publishers, 51 Madison Ave., New York City (10010), 1973. 388 pages, $8.95.

THE DICTIONARY OF SODIUM, FATS, AND CHOLESTEROL—Barbara Kraus. Grosset & Dunlap Publishers, 51 Madison Ave., New York City (10010), 1974. 366 pages, $9.95.

DON'T FEEL SORRY FOR PAUL—Written and Photographed by Bernard Wolf. J. B. Lippincott Co., 521 Fifth Ave., New York City (10017), 1974. 96 pages, $6.95.

EDWARD J. KEMPF—SELECTED PAPERS—Edited by Dorothy Clarke Kempf, MD, formerly Assistant Physician, St. Elizabeth's Hospital, Washington DC; and John C. Burnham, PhD, Professor of History and Lecturer in Psychiatry, Ohio State University. Indiana University Press, Bloomington (47401), 1974. 402 pages, $15.00.

EVALUATIONS OF DRUG INTERACTIONS—1973—American Pharmaceutical Association with assistance of ADA, AMA, ASHP, FDA, end the National Library of Medicine. American Pharmaceutical Association, 2215 Constitution, N.W., Washington DC (20037), 1973. 357 pages, $10.00. **EVALUATIONS OF DRUG INTERACTIONS—1974 Supplement**—American Pharmaceutical Association, 2215 Constitution Avenue, N.W., Washington, DC (20037), 1974. 70 pages, $2.00.

THE FIGHT FOR LAETRILE VITAMIN B17—Forbidden Weepon Against Cancer—Michael L. Culbert. Arlington House Publishers, New Rochelle, N.Y., 1974. 212 pages, $8.95.

GENERAL OPHTHALMOLOGY—Seventh Edition—Daniel Vaughan, MD, Associate Clinical Professor of Ophthalmology, University of California, San Francisco, School of Medicine; and Taylor Asbury, MD, Professor and Director, Department of Ophthalmology, College of Medicine, University of Cincinnati. Lange Medical Publications, Drawer L, Los Altos, CA (94022), 1974. 334 pages, $9.50.

THE PRIVATE LIFE OF ISLAM—Ian Young, MD. W. W. Norton & Company, Inc., 500 Fifth Avenue, New York City (10036), 1974. 308 peges, $8.95.

PROBLEMS IN LAW AND MEDICINE—Volume Seven, 1974, University of California, Davis Law Review—Tracy S. Rich, Editor-in-Chief. School of Law, Martin Luther King, Jr., Hall, University of California, Davis, Davis, CA 95616 (Copyright: Regents of the University of California), 1974. 567 pages, $12.00 (California residents add 72¢ sales tax).

SURGERY OF REPAIR AS APPLIED TO HAND INJURIES—Fourth Edition—B. K. Rank, Kt, CMG, MS(Melbourne), FRCS(Englend end Cenede), Consulting Plastic Surgeon, Royal Melbourne Hospital; A. R. Wekefield, MS(Melbourne), FRCS(England), Formerly Plastic Surgeon, Royel Children's Hospital, Melbourne, and J. T. Hueston, MS(Melbourne), FRCS (England), Honorary Plastic Surgeon, The Royal Melbourne Hospitel. Longmen Inc., 72 Fifth Avenue, New York City (10011), 1973. 390 pages, $15.00.

CONTINUING MEDICAL EDUCATION

California, Hawaii • Oregon • Washington, Montana, Alaska, Idaho

CALIFORNIA and HAWAII

COMMITTEE ON CONTINUING MEDICAL EDUCATION

THIS BULLETIN of information regarding continuing education programs and meetings of various medical organizations in **California and Hawaii** is supplied by the Committee on Continuing Medical Education of the California Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Committee on Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103; or phone (415) 777-2000. Note: Please see **California Medicine**, Vol. 117, No. 4, October, 1972 issue for a list of organizations approved for Category I Credit toward the CMA Certificate in Continuing Medical Education.

CANCER

February 27-March 2—**Seminar on Modern Concepts in Oncology—3rd Annual.** UCLA. Thursday-Sunday.

February 28—**Cancer of the Head and Neck.** American Cancer Society, Kern County Unit, at Bakersfield Inn, Bakersfield. Friday. 7 hrs. $25. Contact: Donald C-S Tan, MD and/or Phillip Mahans, DDS, Co-Chairmen, 238 18th St., Bakersfield 93301. (805) 325-5117.

March 20-21—**Clinical Cancer Conference—10th Annual.** UCSF at St. Francis Hotel, San Francisco. Thursday-Friday.

MEDICINE

February 15-19—**American Academy of Allergy.** Town and Country Hotel, San Diego. Saturday-Wednesday. Contact: Janice Manke, AAA, 225 E. Michigan St., Milwaukee, Wis. 53202. (415) 272-6071.

February 19—**Cardiopulmonary Resuscitation.** Charles R. Drew Postgraduate Medical School at Martin Luther King, Jr., General Hospital, Los Angeles. Wednesday. Contact: Office of Continuing Education, Drew Postgraduate Medical School, 1621 E. 120th St., Los Angeles 90059. (213) 564-5911, ext. 391.

February 19—**Symposium on Endocrinology.** N. T. Enloe Memorial Hospital at Holiday Inn, Chico. Wednesday. 6 hrs. $20. Contact: Mr. John Behrman, Asst. Admin., N. T. Enloe Memorial Hospital, 5th Ave. and Esplanade, Chico 95926. (916) 342-1841.

February 21-22—**Allergy and Immunology/Dermatology Symposium.** So. Calif. Permanente Medical Group at Hilton Hotel, Los Angeles. Friday-Saturday. Contact: Shirley Gach, So. Calif. Permanente Med. Group, 4900 Sunset Blvd., Los Angeles 90027. (213) 667-4241.

February 21-22—**American College of Physicians, Southern California Regional Meeting.** Convention Center, Los Angeles. Friday-Saturday. Contact: Walter P. Martin, MD, 21510 S. Main St., Carson 90745.

February 26-28—**Acute Respiratory Care.** California Thoracic Society at Beverly Hilton Hotel, Beverly Hills. Wednesday-Friday. 21 hrs. $135 for CTS members; $160, others. Contact: Mrs. Laurie Harkess, Prog. Asst., CTS, 224 Pendleton Way, Oakland 94621. (415) 636-1756.

February 27-28—**Endocrinology.** USC at Good Samaritan Hospital, Los Angeles. Thursday-Friday.

February 27-28—**Dermatology for Internists and GPs.** UCSF. Thursday-Friday.

March 1—**Echocardiography Workshop.** PMC. Saturday. $65.

March 4—**Cutaneous Medicine.** USC. Tuesday.

March 6-8—**Cardiovascular Disease—1975: Practical Diagnosis and Management.** American College of Cardiology at Sheraton Harbor Island Hotel, San Diego. Thursday-Saturday. Contact: Mary Anne McInerny, Dir., Dept. of Cont. Ed. Programs, 9650 Rockville Pike, Bethesda, Md. 20014. (301) 530-1600.

March 7—**Diabetes.** USD at Sacramento Inn, Sacramento. Friday.

March 10-14—**Electrophysiology.** USC at Canyon Club, Palm Springs. Monday-Friday.

March 12—**Hematology Symposium.** N. T. Enloe Memorial Hospital at Holiday Inn, Chico. Wednesday. 6 hrs. $20. Contact: Mr. John Berhman, Asst. Admin., N. T. Enloe Memorial Hospital, 5th Ave. and Esplanade, Chico 95926. (916) 342-1841.

KEY TO ABBREVIATIONS AND SYMBOLS

Medical Centers and CMA Contacts for Information

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103. (415) 777-2000.

LLU: Loma Linda University
Contact: John E. Peterson, MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311.

PMC: Pacific Medical Center
Contact: Allen J. Enelow, MD, Chairman, Education Committee, Pacific Medical Center, P.O. Box 7999, San Francisco 94120. (415) 563-4321.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Neil C. Andrews, MD, Chairman, Department of Postgraduate Medicine, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, California College of Medicine, Irvine
Contact: Robert Combs, MD, Associate Dean, Continuing Medical Education, University of California, Irvine—California College of Medicine, Irvine 92664. (714) 833-5991.

UCLA: University of California, Los Angeles
Contact: Donald Brayton, MD, Director Continuing Education in Medicine and the Health Sciences. P.O. Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: Richard A. Lockwood, MD, Associate Dean for Health Manpower, 1310 Basic Sciences Building, University of California, San Diego, School of Medicine, La Jolla 92037. (714) 453-2000, ext. 1251.

UCSF: University of California, San Francisco
Contact: Malcolm S. M. Watts, MD, Associate Dean and Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-2342.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 226-2047.

March 13-14—**Core Curriculum: Cardiovascular Physiology: Clinical Implications of Newer Concepts and Measurements.** American College of Cardiology and UCLA at Cedars of Lebanon Hospital, Los Angeles. Thursday-Friday. Contact: Mary Anne McInerny, Dir., Dept. of Cont. Ed. Programs, ACC, 9650 Rockville Pike, Bethesda, Md. 20014. (301) 530-1600.

March 13-15—**Cardiology '75.** American Heart Association, Golden Empire Chapter, at Sahara Tahoe Hotel, South Lake Tahoe. Thursday-Saturday. Contact: Nemat O. Borhani, MD, P.O. Box 16011, Sacramento 95816.

March 15-16—**Echocardiography.** UCLA. Saturday-Sunday.

March 20-21—**Arthritis and Clinical Immunology.** USC. Thursday-Friday.

March 21—**Cerebrovascular Disease: Prevention and Diagnosis.** PMC. $60.

March 21-22—**Infectious Disease.** UCLA. Friday-Saturday.

March 27-29—**Recent Advances in Coronary Heart Disease.** UCI and Pasadena Cardiovascular Research Foundation at Balboa Bay Club, Newport Beach. Thursday-Saturday.

March 31-April 11—**Intensive Review of Internal Medicine.** USC. Two weeks.

April 2—**Sudden Death and Coronary Disease: Diagnostic and Therapeutic Interventions—12th Annual Spring Symposium.** American Heart Association-Greater Los Angeles Affiliate at Beverly Hilton Hotel, Beverly Hills. Wednesday. Contact: LaVerna Titus, AHA-Greater L.A. Affiliate, 2405 W. 8th St., Los Angeles 90057. (213) 385-4231.

April 3-4—**California Thoracic Society.** Sheraton Inn-Harbor Island Hotel, San Diego. Thursday-Friday. Contact: Laurie Harkness, CTS, 224 Pendleton Way, Oakland 94621. (415) 636-1756.

April 6-9—**What's New in Gastroenterology.** UCLA at Canyon Hotel, Palm Springs. Sunday-Wednesday.

April 7-10—**American College of Physicians—56th Annual Session.** Fairmont Hotel, San Francisco. Monday-Thursday. Contact: Edward C. Rosenow, Jr., MD, Exec. VP, ACP, 4200 Pine St., Philadelphia, Pa. 19104. (215) 222-8120.

April 7-16—**Cardiology for the Consultant: A Clinician's Retreat.** American College of Cardiology at Rancho Santa Fe Inn, Rancho Santa Fe. 10 days. Contact: Mary Anne McInerny, Dir., Dept. of Cont. Ed. Programs, 9650 Rockville Pike, Bethesda, Md. 20014. (301) 530-1600.

April 13-14—**American College of Physicians, Hawaii Regional Meeting.** Honolulu. Sunday-Monday. Contact: Bernard W. D. Fong, MD, 97 Dowsett Ave., Honolulu 96817.

April 15-18—**Consultants' Course in Dermatology.** UCSF. Tuesday-Friday.

April 21-25—**Diagnostic and Therapeutic Skills in Internal Medicine.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. Monday-Friday.

April 23—**Symposium on Cardiovascular Disease—15th Annual.** Calif. Heart Association and N. T. Enloe Memorial Hospital at Elks Lodge Hall, Chico. Wednesday. 6 hrs. $25. Contact: Marge Herman, CHA, 1372 Longfellow Ave., Chico 95926. (916) 342-4247.

MENTAL RETARDATION

March 9-21—**Mental Retardation.** UCLA. 13 days.

April 29-30—**Mental Retardation.** USC. Tuesday-Wednesday.

OBSTETRICS AND GYNECOLOGY

March 7-8—**Current Topics in Contraception: The Pill vs. IUD.** PMC at Miyako Hotel, San Francisco. Friday-Saturday.

March 15-16—**Gynecologic Endoscopy: Diagnostic and Operative.** UCI and American Association of Gynecological Laparoscopists. Saturday-Sunday. $150.

March 25-28—**High Risk Pregnancy.** USC at Canyon Hotel, Palm Springs. Tuesday-Friday.

March 28-29—**Review of Gynecological Surgery.** PMC at Miyako Hotel, San Francisco. Friday-Saturday.

April 2-5—**American Fertility Society.** Century Plaza Hotel, Los Angeles. Wednesday-Saturday. Contact: Robert B. Wilson, MD, Med. Dir., AFS, 1608 13th Ave. S., Suite 101, Birmingham, Ala. 35205. (205) 933-7222.

April 16-18—**Association of Planned Parenthood Physicians.** See Of Interest to All, April 16-18.

April 21-25—**Family Planning.** UCLA. Monday-Friday. Contact: Irvin M. Cushner, MD, Ob-Gyn Dept., UCLA Center for Health Sciences, Los Angeles 90024. (213) 825-1046.

PEDIATRICS

February 27-March 1—**Pediatric Emergencies.** Children's Hospital Medical Center at Sahara Tahoe Hotel, South Lake Tahoe. Thursday-Saturday. 9 hrs. $75. Contact: Inetta Carty Calori, Med. Staff Adm. Asst., CHMC, 51st and Grove Sts., Oakland. (415) 654-5600.

March 7-9—**Clinical Pediatrics—5th Annual Southern California Pediatric Postgraduate Course.** Am. Academy of Ped., Chapter II, Dist. 9; Childrens Hosp. of L.A.; L.A. Ped. Soc.; Southwest Ped. Soc.; Childrens Hosp. of Orange Co. at Riviera Hotel, Palm Springs. Friday-Sunday. $75. Contact: Robert M. Romans, MD, c/o Lili Crellin, Resident's Office, Childrens Hospital, 4650 Sunset Blvd., L.A. 90027.

March 8-9—**Health of the School Child.** UCSF. Saturday-Sunday.

April 4-5—**Pediatric Conference: Infectious Diseases and Adolescent Medicine.** UCD at Mansion Inn, Sacramento. Saturday-Sunday.

April 5-12—**Pediatrics.** USC at Kona Surf Hotel, Kona, Hawaii. One week.

April 21-25—**Review of Pediatrics.** USC. Monday-Friday.

April 26—**Growth to Maturity: The Adolescent and the Helping Professions.** UCSF. Saturday.

PSYCHIATRY

February 28-March 1—**Community Mental Health.** USC at Continental Hyatt House, Hollywood. Friday-Saturday. 10 hrs. $60. Contact: Donald H. Naftulin, MD, Dir., Cont. Ed. in Psych., USC. (213) 226-2114.

April 9-June 25—**Advanced Psychotherapeutic Techniques—A Practical Approach to Therapy—Part II.** UCLA. Wednesdays, 7:30-10:00 p.m.

April 25—**Prevention and Indirect Services.** See Of Interest to All, April 25.

RADIOLOGY AND PATHOLOGY

February 15-16—**Diagnostic Nuclear Imaging: A Review and What's New.** UCSF at Fairmont Hotel, San Francisco. Saturday-Sunday.

February 17-21—**Diagnostic Radiology.** UCSF at Fairmont Hotel, San Francisco. Monday-Friday.

February 22-23—**A Practical Course in Ultra Sound.** UCSF at Fairmont Hotel, San Francisco. Saturday-Sunday.

SURGERY AND ANESTHESIOLOGY

February 15—**Sports Injuries to the Knee.** Charles R. Drew Postgraduate Medical School at Martin Luther King, Jr., General Hospital, Los Angeles. Saturday. Contact: Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 E. 120th St., Los Angeles 90059. (213) 564-5911, ext. 391.

February 15—**Surgical Anatomy and Surgery of the Neck.** International College of Surgeons, U.S. Section, at L.A. Orthopaedic Hospital, Los Angeles. Saturday. 8 hrs. $50. Contact: Irving Rehman, PhD, Chr., Postgraduate & Ongoing Education Committee, 5153 Tampa Ave., Tarzana 91356. (213) 344-3305.

February 15-21—**Pan-Pacific Surgical Association—13th Congress.** Hilton Hawaiian Village Hotel, Honolulu. Saturday-Friday. 22½ hrs. Contact: Robert A. Rose, MD, Sec. Gen., Pan-Pacific Surgical Assn., 236 Alexander Young Building, Honolulu 96817. (808) 536-4911.

February 19—**Cardiopulmonary Resuscitation.** See Medicine, February 19.

February 19-21—**Critical Care Medicine and Circulatory Shock.** See Of Interest to All, February 19-21.

February 23-March 7—**Temporal Bone Surgical Dissection Course.** Ear Research Institute, Los Angeles. Two weeks. $1,200; $900 for residents. Contact: Jack L. Pulec, MD, Ear Research Institute, 2130 W. 3rd St., Los Angeles 90057.

February 26-28—**Acute Respiratory Care.** See Medicine, February 26-28.

February 27-March 1—**American Society for Surgery of the Hand—Annual Meeting.** Fairmont Hotel, San Francisco. Thursday-Saturday. $50. Contact: John A. Boswick, Jr., MD, 4200 E. 9th Ave., #2414, Denver 80220. (303) 394-8549.

February 27-March 1—**Orthopaedic Research Society—21st Annual Meeting.** Civic Auditorium, San Francisco. Thursday-Saturday. Registration Feb. 26, 6-9 p.m., S.F. Hilton; Feb. 27-28, 7:30-8:30 a.m., Larkin Hall Corridor, Civic Auditorium. (No pre-registration.)

February 28—**The Hip Society—3rd Scientific Meeting.** Civic Auditorium, San Francisco. Friday. Registration Feb. 27, 3-6 p.m.; Feb. 28, 7 a.m.-noon. (No pre-registration.)

February 28-March 2—**Harry Benjamin 4th International Conference on Gender Identity.** STAN. Friday-Sunday.

March 1—**American Orthopaedic Foot Society—Annual Scientific Meeting.** Veterans Memorial Building, San Francisco. Saturday. Contact: Henry R. Cowell, MD, Box 269, Wilmington, Dela. 19805. (302) 571-1000.

March 1-6—**American Academy of Orthopaedic Surgeons.** Brooks Hall, Civic Auditorium, San Francisco. Friday-Wednesday. Contact: Charles V. Heck, MD, Exec. Dir., AAOS, 430 N. Michigan Ave., Chicago, Ill. 60611. (312) 822-0970.

March 6—**American Orthopaedic Society for Sports Medicine.** Hilton Hotel, San Francisco. Thursday. Contact: Leslie M. Bodnar, MD, 328 N. Michigan Ave., South Bend, Ind. 46601.

March 11-15—**Symposium on Vascular Surgery—3rd Annual.** UCLA at Canyon Hotel, Palm Springs. Tuesday-Saturday.

March 12-15—**Neurosurgical Society of America.** Rancho Bernardo, San Diego. Wednesday-Saturday. Contact: Shelley N. Chou, MD, U. of Minn. Medical School, Minneapolis, Minn. 55455.

March 13-14—**Phaco-Fragmentation.** UCSF. Thursday-Friday.

March 15—**Surgical Anatomy and Surgery of the Abdomen.** International College of Surgeons, U.S. Section, at L.A. Orthopaedic Hospital, Los Angeles. Saturday. 8 hrs. $50. Contact: Irving Rehman, PhD, Chr., Postgraduate & Ongoing Education Committee, 5153 Tampa Ave., Tarzana 91356. (213) 344-3305.

March 15-16—**Los Angeles County Society of Anesthesiologists—20th Annual Postgraduate Assembly.** Hilton Hotel, Los Angeles. Saturday-Sunday. Contact: L.A. County Soc. of Anesthesiologists, 184 N. Canon Dr., Beverly Hills 90210.

March 15-19—**Controversial Areas in Surgery—12th Annual.** UCLA at Canyon Hotel, Palm Springs. Saturday-Wednesday.

March 16-28—**Temporal Bone Surgical Dissection Course.** Ear Research Institute, Los Angeles. Two weeks. $1,200; $900, residents. Contact: Jack L. Pulec, MD, 2130 W. 3rd St., L.A. 90057.

March 19-23—**Management of Trauma.** UCLA at Canyon Hotel, Palm Springs. Wednesday-Sunday.

March 20-21—**Diseases of the Urinary Tract: Techniques and Principles of Urologic Surgery—3rd Annual Symposium.** STAN. Thursday-Friday.

April 3-4—**Ophthalmology Symposium—Posterior Segment Complications of Anterior Segment Surgery.** Mt. Zion Hospital and Medical Center at St. Francis Hotel, San Francisco. Thursday-Friday. 16 hrs. $200. Contact: Linda Cross, Dept. of Cont. Ed., Mt. Zion Hospital, 1600 Divisadero, San Francisco 94115. (415) 567-6600, ext. 108.

April 3-4—**California Thoracic Society.** See Medicine, April 3-4.

April 5-12—**Orthopedics.** USC at Mauna Kea Hotel, Kamuela, Hawaii. One week.

April 6-18—**Temporal Bone Surgical Dissection Course.** Ear Research Institute, Los Angeles. Two weeks. $1,200; $900 for residents. Contact: Jack L. Pulec, MD, Ear Research Institute, 2130 W. 3rd St., Los Angeles 90057.

April 10-12—**General Surgery—Annual Conference.** UCSF at Hilton Hotel, San Francisco. Thursday-Saturday.

April 19—**Surgical and Clinical Anatomy of the Vascular System.** International College of Surgeons, U.S. Section, at L.A. Orthopaedic Hospital, Los Angeles. Saturday. 8 hrs. $50. Contact: Irving Rehman, PhD, Chr., Postgraduate and Ongoing Education Committee, International College of Surgeons, U.S. Section, 5153 Tampa Ave., Tarzana 91356. (213) 344-3305.

April 24-25—**Phaco-Fragmentation.** UCSF. Thursday-Friday.

April 26-May 3—**Management of the Surgical Patient.** STAN at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week.

OF INTEREST TO ALL PHYSICIANS

February 16-19—**Society of Critical Care Medicine.** Anaheim. Sunday-Wednesday. Contact: David Allan, MD, Children's Memorial Hospital, 2300 Children's Plaza, Chicago, Ill. 60614.

February 19-21—**Critical Care Medicine and Circulatory Shock.** USC at Anaheim Convention Center, Anaheim. Wednesday-Friday.

February 21-22—**The Process and Treatment of Aging.** Vista Hill Foundation at Hilton Inn, San Diego. Friday-Saturday. $35; $20 for students and interns. Contact: Keith S. Ditman, MD, Vista Hill Foundation, 7798 Starling Dr., Suite 206, San Diego 92123. (714) 278-6761.

February 21-26—**California Medical Association—104th Annual Session.** Los Angeles Convention Center. Friday-Wednesday.

February 27-28—**Dermatology for Internists and GPs.** See Medicine, February 27-28.

February 28-March 2—**Harry Benjamin 4th International Conference on Gender Identity.** See Surgery, February 28-March 2.

March 3-7—**Basic Science for Clinicians.** STAN. Monday-Friday.

(Continued on Page 39)

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References: 1. Batterman, R.C., and Grossman, A.J.: Fed. Proc. *14*:316, 1955. **2.** Goodman, L.S., and Gilman, A., ed.: The Pharmacological Basis of Therapeutics, ed. 4. New York, The Macmillan Company, 1970. **3.** Vickers, F.N.: Gastroint. Endosc. *14*:94, 1967. **4.** Mielke, C.H., Jr., and Britten, A.F.H.: New Engl. J. Med. *282*:1270, 1970 (Corresp.). **5.** Vernon, W.G.: Curr. Therap. Res. *14*:801, 1972. **6.** Scheiner, J.J.: Curr. Therap. Res. *14*:168, 1972. **7.** Walker, J.M.: Curr. Therap. Res. *15*:248, 1973. **8.** Data on file, McNeil Laboratories, Inc.

† U.S. Patent No. 2,895,877

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Fort Washington, Pa. 19034

(Continued from Page 37)

March 9-13—**LLU Alumni Postgraduate Convention.** Sunday-Thursday. 23 hrs. $100. Contact: Gerald W. Miller, Gen. Chr., 1832 Michigan, Los Angeles. (213) 262-2173.

March 13-16—**Continuing Education in the Physician's Office.** USC at Mayer Auditorium, Palm Springs. Thursday-Sunday.

March 21-22—**West Coast Counties Postgraduate Institute.** CMA at Quail Lodge, Carmel. Friday-Saturday.

March 23-27—**American Association of Anatomists.** Hilton Hotel, Los Angeles. Sunday-Thursday. Contact: Dr. Melvin Hess, Dept. of Anatomy, La. State Univ. Med. Center, 1542 Tulane Ave., New Orleans, La. 70112.

April 6-10—**The Family in Family Practice.** UCLA at Riviera Hotel, Palm Springs. Sunday-Thursday.

April 13-17—**American Industrial Health Conference.** American Occupational Medical Association at Hilton Hotel, San Francisco. Sunday-Thursday. 18 hrs. $30. Contact: Howard N. Schulz, Exec. Dir., AOMA, 150 N. Wacker Dr., Chicago, Ill. 60606. (312) 782-2166.

April 16-18—**Association of Planned Parenthood Physicians—13th Annual Scientific Meeting and Postgraduate Program.** Century Plaza Hotel, Los Angeles. Wednesday-Friday. Contact: Joseph E. Davis, MD, 810 7th Ave., N.Y. 10019. (212) 541-7800.

April 17-18—**Obesity.** USC. Thursday-Friday.

April 19-20—**Ethical Issues in Modern Medical Practice.** UCLA. Saturday-Sunday.

April 21-25—**Emergency Medicine.** USC at Kona Surf Hotel, Kona, Hawaii. Monday-Friday.

April 21-25—**Family Planning.** See Ob-Gyn, April 21-25.

April 21-May 2—**Emergency Department Medicine in Practice.** UCLA and Harbor General Hospital at Harbor Gen. Hosp., Torrance. Two weeks.

April 25—**Prevention and Indirect Services.** Kings View Foundation at Sheraton Inn, Fresno. Friday. $20. Directed to physicians interested in various aspects of prevention in fields of mental health, developmental disabilities, substance abuse and gerontology. Contact: Kings View Foundation, Public Information Dept., P.O. Box 512, Reedley 93654. (209) 638-3655.

April 25-27—**Advances in the Control & Management of Chronic Pain.** UCLA. Friday-Sunday.

April 28-May 1—**Aerospace Medical Association—46th Annual Scientific Meeting.** Hilton Hotel, San Francisco. Monday-Thursday. 18 hrs. Contact: Merrill H. Goodwin, MD, Exec. VP, Aerospace Med. Assn., Washington National Airport, Washington, D.C. 20001. (202) 638-2190.

PRECEPTORSHIPS AND TRAINEESHIPS

Training for Physicians in General Internal Medicine. LLU. Four weeks or more, by arrangement. Bedside and classroom training, practical aspects of clinical care and management. 160 hrs. Contact: John E. Peterson, MD, LLU.

Training of Physicians in Modern Concepts of Pulmonary Care. LLU. Four weeks or more, by arrangement. Diagnostic and therapeutic methods in medical chest disease, physiological methodology of modern pulmonary care programs, use of new instrumentation in the field. 160 hrs. Contact: John E. Hodgkin, MD, Chief, Section of Medical Chest Diseases, LLU.

Training for Physicians in Nephrology. LLU. Four weeks or more, by arrangement. Hemodialysis, peritoneal displays, renal biopsy, and kidney transplantation. 160 hrs. Contact: Robert E. Soderblom, MD, LLU.

Mini Residencies in Orthopaedics. STAN. Postgraduate traineeships of 4-14 days, as you wish. No tuition but donations accepted. Contact: Orthopaedic Division, Dept. of Surgery, Stanford.

Preceptorships in Cardiology. PMC. By arrangement. $200 per mo.; $500 for 3 mos. Contact: Arthur Selzer, MD, PMC.

Preceptorships in Practical Office Dermatology. PMC. Wednesdays or Fridays, 9:00 a.m.-12:00 noon, for 10 weeks. Periods begin Oct., Jan., or April. $100. Contact: Harold M. Schneidman, MD, Dept. of Dermatology, PMC.

Preceptorships in Infectious Disease. PMC. Full time for four weeks. To be arranged. $250. Contact: Rodney J. Valentine, MD, Chief, Div. of Infectious Diseases, PMC.

Preceptorships in Basic Sciences, Biochemistry and Biophysics, Dermatology, International Health, Microbiology, Neurological Surgery, Obstetrics and Gynecology, Pediatrics, Pharmacology and Experimental Therapeutics, Physiology, Psychiatry, Urology. UCSF. By special arrangement.

Traineeships in Renal Dialysis. UCSF. By special arrangement.

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OREGON

COUNCIL ON MEDICAL EDUCATION

THIS BULLETIN of information regarding continuing education programs and meetings of various medical organizations in Oregon is supplied by the Council on Medical Education of the Oregon Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Council on Medical Education, Oregon Medical Association, 2164 S.W. Park Place, Portland, Oregon 97205; or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

University of Oregon Medical School, Family Practice Center, 3181 S.W. Sam Jackson Park Road, Portland 97201:

Every Thursday, 8:00 a.m. to 9:00 a.m.—**Family Practice Grand Rounds.** Contact: David D. Smith, MD, Department of Family Practice, University of Oregon Medical School.

CARDIOLOGY

June 5-7—**Progress in Coronary Artery Disease and Valvular Heart Disease,** Portland. Contact: S H. Rahimtoola, University of Oregon Medical School, 3181 S.W. Sam Jackson Park Road, Portland, 97201.

FAMILY PRACTICE

Every Thursday, 8:00 a.m. to 9:00 a.m.—**Family Practice Grand Rounds,** Family Practice Center, University of Oregon Medical School, Portland. Contact: David D. Smith, MD, Department of Family Practice, University of Oregon Medical School, 3181 S.W. Sam Jackson Park Road, Portland 97201.

OF INTEREST TO ALL PHYSICIANS

May 30-31—**Hypertension: The Challenge to the Clinician,** Portland, Jantzen Beach Thunderbird. Sponsored by the University of Oregon Medical School. Contact: M. Roberts Grover, Jr., MD, Associate Dean, University of Oregon Medical School, 3181 SW Sam Jackson Park Road, Portland 97201, (503) 225-8228. Acceptable for 10 hours Category I credit.

WASHINGTON, MONTANA, ALASKA and IDAHO

In order to have future activities listed here or to receive information on these and other activities, please write Ms. Joan M. Kelday, Information Specialist, Continuing Medical Education, WAMI Program, University of Washington School of Medicine, E-301, Health Sciences Building, SC-45, Seattle, Washington 98195. Phone: (206) 543-6995.

February 19-20 — **Trauma-Burns-Shock: Emergency Medical Care—Univ. of Washington School of Medicine's Western Circuit Course.** Longview, Wash., Feb. 19; Olympia, Wash., Feb. 20. 4 hrs. $25. Contact: Richard L. Reimer, Asst. Dir. CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

February 20-21—**Thirteenth Annual Symposium on Respiratory Disease.** Thursday-Friday. Olympic Hotel, Seattle. 14 hrs. $10. Contact: Richard L. Reimer, Asst. Dir. CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

February 28-March 1—**The Intensive Care Patient.** Friday-Saturday. Virginia Mason Medical Center Auditorium, Seattle. 9 hrs. $50. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) MA 3-3700, Ext. 470.

March 4-5—**Trauma-Burns-Shock: Emergency Medical Care—Univ. of Washington School of Medicine's Western Circuit Course.** Bremerton, Wash., Mar. 4; Bellingham, Wash., Mar. 5. 4 hrs. $25. Contact: Richard L. Reimer, Asst. Dir. CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

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- **FOR PROGRAM INFORMATION CALL (415) 666-4251**

March 14-15—**Current Concepts in Cardiology.** Friday-Saturday. Virginia Mason Medical Center Auditorium, Seattle. 9 hrs. $50. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) MA 3-3700, Ext. 470.

March 17-21—**Emergency Medicine Institute.** Monday-Friday. Univ. of Wash. Health Sciences Center, Seattle. 40 hrs. $250. Contact: Richard L. Reimer, Asst. Dir. CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

March 20-21—**Basic Sciences for Clinicians.** Thursday-Friday. Univ. of Wash. Health Sciences Center, Seattle. Hours and fee not set. Contact: Richard L. Reimer, Asst. Dir. CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

March 31-April 4—**Advances in Family Practice.** Monday-Friday. Univ. of Wash. Health Sciences Center, Seattle. 40 hrs. $100. Contact: Richard L. Reimer, Asst. Dir. CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

April 4-5—**Acid Base and Blood Gas Management in the Surgical Patient.** Friday-Saturday. Virginia Mason Medical Center Auditorium, Seattle. 9 hrs. $50. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) MA 3-3700, Ext. 470.

April 24-25—**Conference on Respiratory Care.** Thursday-Friday. Univ. of Wash. Health Sciences Center, Seattle. Hours not set. $75. Contact: Richard L. Reimer, Asst. Dir. CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

April 28-May 2—**Emergency Medicine Institute.** Monday-Friday. Univ. of Wash. Health Sciences Center, Seattle. 40 hrs. $250. Contact: Richard L. Reimer, Asst. Dir. CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

April 29-30—**Exercise Testing Workshop.** Tuesday-Wednesday. Univ. of Wash. Health Sciences Center, Seattle. Hours and fee not set. Contact: Richard L. Reimer, Asst. Dir. CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

May 14-16—**Advances in Internal Medicine.** Wednesday-Friday. University Tower Hotel, Seattle. 18 hrs. $150. Contact: Richard L. Reimer, Asst. Dir. CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

May 16-17—**Washington Academy of Family Physicians Annual Meeting.** Friday-Saturday. Inn-at-the-Quay, Vancouver, Wash. 10 AAFP hrs. Contact: Walter Lapsley, Exec. Secretary, WAFP, 10003 SE Evergreen Highway, Vancouver, WA 98664.

May 16-17—**Puget Sound Academy of Otolaryngology Annual Meeting.** Friday-Saturday. Olympic Hotel, Seattle. Contact: Joseph W. Walike, MD, 1118 9th Ave., Seattle 98101. (206) 623-3700.

May 22-23—**Pediatric Care for Family Practitioners.** Thursday-Friday. Children's Orthopedic Hospital and Medical Center, Seattle. 12 hrs. $35. Contact: William O. Robertson, MD, Director of Medical Education, Children's Orthopedic Hospital, P.O. Box 5371, Seattle 98105. (206) 634-5072.

May 25-27—**Alaska State Medical Association Annual Meeting.** Sunday-Tuesday. Glacier Bay, Alaska. Contact: Mrs. Martha L. MacDermaid, Alaska State Medical Assoc., 1135 8th Ave., Anchorage, Alaska 99501.

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Predominant psychoneurotic anxiety

Associated depressive symptoms

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Tension and anxiety states; somatic complaints which are concomitants of emotional factors; psychoneurotic states manifested by tension, anxiety, apprehension, fatigue, depressive symptoms or agitation; symptomatic relief of acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in skeletal muscle spasm due to reflex spasm to local pathology, spasticity caused by upper motor neuron disorders, athetosis, stiff-man syndrome, convulsive disorders (not for sole therapy).

Contraindicated: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms (similar to those with barbiturates and alcohol) have occurred following abrupt discontinuance (convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Keep addiction-prone individuals under careful

respond to one

According to her major symptoms, she is a psychoneurotic patient with severe anxiety. But according to the description she gives of her feelings, part of the problem may sound like depression. This is because her problem, although primarily one of excessive anxiety, is often accompanied by depressive symptomatology. Valium (diazepam) can provide relief for both—as the excessive anxiety is relieved, the depressive symptoms associated with it are also often relieved.

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Also, because the psychoneurotic patient's symptoms are often intensified at bedtime, Valium can offer an additional benefit. An *h.s.* dose added to the *b.i.d.* or *t.i.d.* treatment regimen can relieve the excessive anxiety and associated depressive symptoms and thus encourage a more restful night's sleep.

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2-mg, 5-mg, 10-mg tablets

in psychoneurotic anxiety states with associated depressive symptoms

surveillance because of their predisposition to habituation and dependence. In pregnancy, lactation or women of childbearing age, weigh potential benefit against possible hazard.

Precautions: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed; drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.

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"Entered as second class matter at the post office in San Francisco and additional mailing offices under the Act of March 3, 1879." Acceptance for mailing at special rate of postage provided for in Section 1103, Act of October 3, 1917, authorized August 10, 1918.

You helped keep this man in business, Doctor.

Before he was injured he was a traveling salesman. Now he's his own boss.

Charles Foster, working as a driver/salesman for a Sacramento beverage firm, sustained a number of severe injuries when his car overturned in September 1968. A compression fracture of the vertebrae with cord injury made him paraplegic, and ended his career on the road.

But a good salesman never quits, and neither did Charles. He was determined to return to work, and State Fund was determined to help him. During his initial period of intensive care, State Fund worked closely with Charles' doctors to set up a long-range program of health care. At one point Charles' struggle nearly ended in tragedy, when he suffered a cardiac arrest during spinal surgery. But thanks to the skill of the surgical team, he was successfully resuscitated and continued to improve.

Today, thanks to the expert attention of his doctors and with financial assistance from State Fund, Charles has won his fight to live and is a successful businessman. With a partner, also paraplegic, he operates The Wheelchair Boutique in Sacramento, specializing in sales, repair, and rental of hospital equipment.

At State Fund, we're proud to help people like Charles Foster, people of courage and determination, to rebuild their lives. And we're proud of you too, Doctor.

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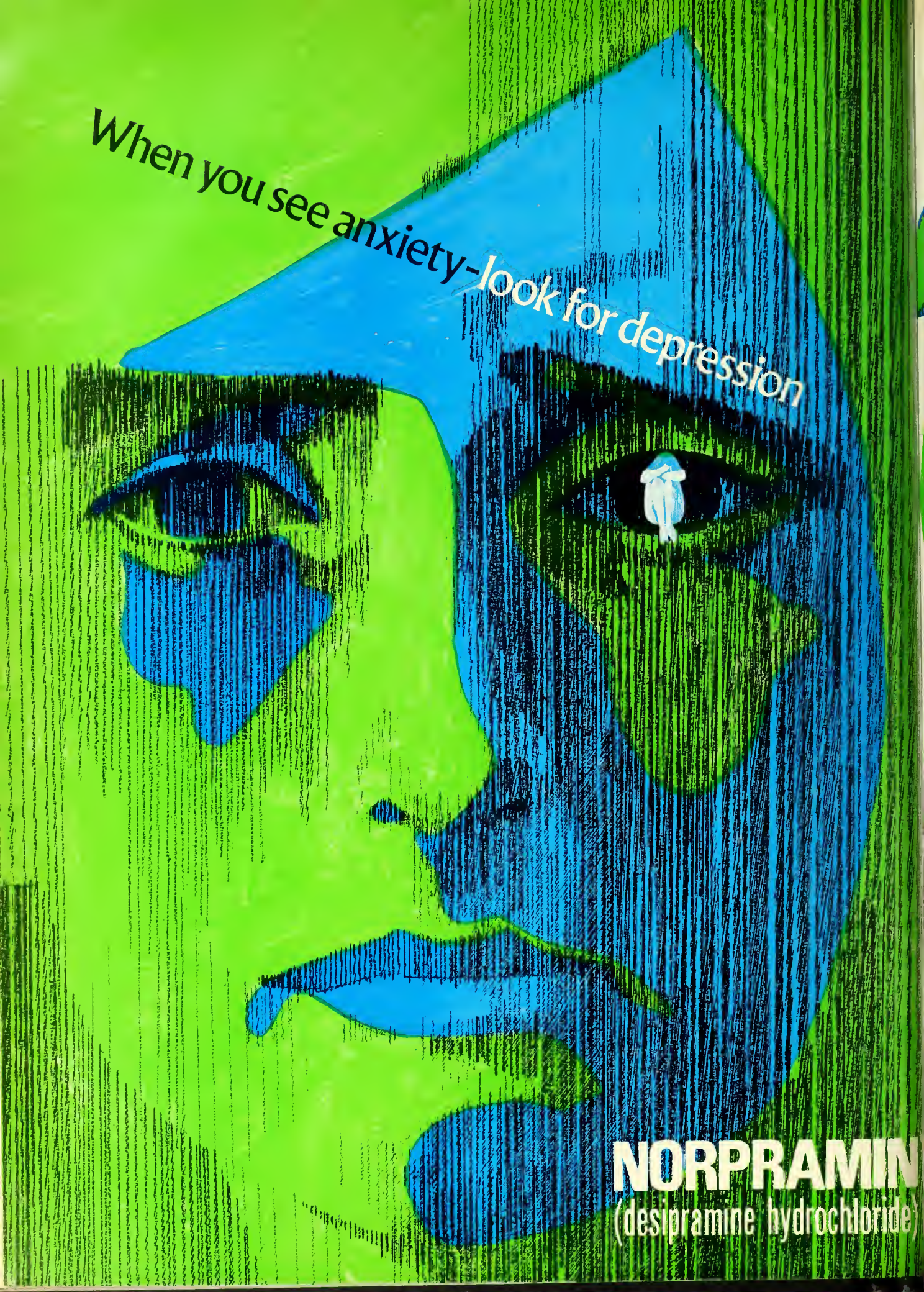
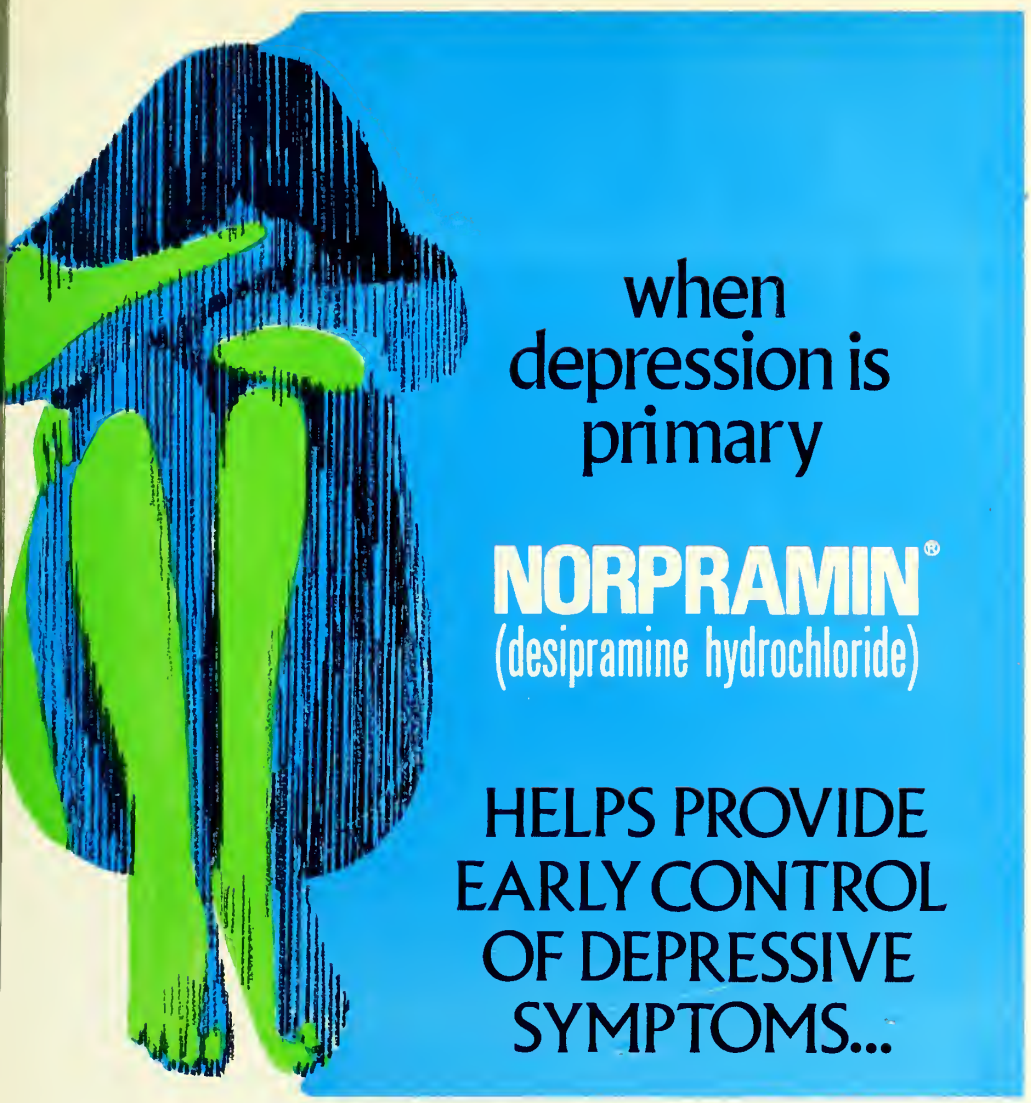

When you see anxiety-look for depression
NORPRAMIN
(desipramine hydrochloride)



Anxiety is an invidious symptom. It feeds upon sickness, gnaws, grows and invades every cranny of psychic pathology adding intensity to torment. Anxiety as a symptom secondary to depression may be so dominant that it obscures the primary diagnosis. It may suggest treatment with tranquilizers which often help. But as the vampire of legend had to have a laurel stake driven through its heart to truly die, so anxiety secondary to depression will not cease to nibble and bite until an antidepressant eradicates the primary illness—and symptomatic anxiety starves.

IN BRIEF:

Indications: Norpramin® (desipramine hydrochloride) is indicated for the relief of depressive symptoms. Endogenous depressions are more likely to be alleviated than others.

Contraindications: Desipramine hydrochloride should not be given within two weeks of treatment with a monoamine oxidase inhibitor. Contraindications include the acute recovery period following myocardial infarction and hypersensitivity to the drug. Cross sensitivity with other dibenzazepines is a possibility.

Warnings: 1. Extreme caution should be used in patients: (a) with cardiovascular disease, (b) with a history of urinary retention or glaucoma, (c) with thyroid disease or those on thyroid medication, (d) with a history of seizure disorder. 2. This drug is capable of blocking the antihypertensive effect of guanethidine and similarly acting compounds. 3. *Use in Pregnancy:* Safe use during pregnancy and lactation has not been established. 4. *Use in Children:* Norpramin® (desipramine hydrochloride) is not recommended for use in children. 5. This drug may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. Therefore, the patient should be cautioned accordingly.

Precautions: This drug should be dispensed in the least possible quantities to depressed outpatients, since suicide has been accomplished with drugs of this class. If possible, dispense in child-resistant containers. It should be kept out of reach of children. Reduce dosage, or alter treatment, if serious adverse effects occur. Norpramin® (desipramine hydrochloride) therapy in patients with manic-depressive illness may induce a hypomanic state after the depressive phase terminates and may cause exacerbation of phychosis in schizophrenic patients. Use cautiously with anticholinergic or sympathomimetic drugs. Response to alcoholic beverages may be exaggerated. In the concurrent administration of ECT and antidepressant drugs one should consider the possibility of increased risk relative to benefits. Discontinue as soon as possible prior to elective surgery because of possible cardiovascular effects. Hypertensive episodes have been observed during surgery in patients on desipramine hydrochloride. Leukocyte and differential counts should be performed in any patient who develops fever and sore throat during therapy; the drug should be discontinued if there is neutropenia.

Adverse Reactions: *Cardiovascular:* hypotension, hypertension, tachycardia, palpitation, arrhythmias, heart block, myocardial infarction, stroke. *Psychiatric:* confusional states (especially in the elderly), hallucinations, disorientation, delusions; anxiety, agitation; insomnia and nightmares; hypomania; exacerbation of phychosis. *Neurological:* paresthesias of extremities; incoordination, ataxia, tremors, peripheral neuropathy; extrapyramidal symptoms; seizures; alteration in EEG patterns; tinnitus. *Anticholinergic:* dry mouth, and rarely associated sublingual adenitis; blurred vision, disturbance of accommodation, mydriasis; constipation, paralytic ileus; urinary retention, delayed micturition, hypotonic bladder. *Allergic:* skin rash, petechiae, urticaria, itching, photosensitization, edema (of face and tongue or general), drug fever. *Hematologic:* agranulocytosis, eosinophilia, purpura, thrombocytopenia. *Gastrointestinal:* anorexia, nausea and vomiting, epigastric distress, peculiar taste, abdominal cramps, diarrhea, stomatitis, black tongue. *Endocrine:* gynecomastia; breast enlargement and galactorrhea in the female; increased or decreased libido, impotence, testicular swelling; elevation or depression of blood sugar levels. *Other:* jaundice (simulating obstructive), altered liver function; weight gain or loss; perspiration, flushing; urinary frequency, nocturia; parotid swelling; drowsiness, dizziness, weakness and fatigue, headache; alopecia. *Withdrawal Symptoms:* Though not indicative of addiction, abrupt cessation after prolonged therapy may produce nausea, headache and malaise.

Dosage and Administration: *The usual adult dose:* 50 mg. three times daily; increase if necessary after 7 to 10 days to maximum of 200 mg. daily. Dosages above 200 mg. per day are not recommended. *Maintenance:* At a lower dose adequate to maintain remission. *Adolescent and geriatric patient dose:* 25 to 50 mg. daily if necessary.

Overdosage: There is no specific antidote for desipramine, nor are there specific phenomena of diagnostic value characterizing poisoning by the drug. The principles of management of coma and shock by means of the mechanical respirator, cardiac pacemaker, monitoring of central venous pressure and regulation of fluid- and acid-base balance are well known in most medical centers. If heart failure is imminent, digitalize promptly.

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In the treatment of clinically significant depression.

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ELAVIL
(AMITRIPTYLINE HCl/MSD)

For highly effective symptomatic relief... the reason to prescribe it

Now added dosage versatility...

℞

ELAVIL
(AMITRIPTYLINE HCl/MSD)

h.S.

- **An important alternative in fitting the medication to the patient's needs**
  Once-a-day dosage at bedtime is an appropriate way to start—and maintain—many patients on therapy. Of course, ELAVIL may be administered two, three, or four times as well as once a day. This dosage versatility allows prescribing precisely for the patient's needs.

- **Once-a-day dosage schedule for adult outpatients**
  Therapy should be initiated with 50 mg to 100 mg at bedtime. This may be increased by 25 or 50 mg added to the bedtime dose as necessary to a maximum daily dose of 150 mg. The usual maintenance dose is 50 to 100 mg a day given at bedtime, though in some patients, 40 mg per day is sufficient.

- **Greater patient compliance**
  The simplicity of once-a-day dosage at bedtime makes it easier for patients to adhere to a regimen—an especially important consideration in depressed patients whose self-motivation may be at a low ebb.

Should not be used during the acute recovery phase following myocardial infarction; in patients hypersensitive to it; in those who have received an MAOI within two weeks; or in children under 12. Patients with cardiovascular disorders should be watched closely. Safe use during pregnancy and lactation has not been established. The drug may impair mental or physical abilities required in the performance of hazardous tasks and may enhance the response to alcohol. Since suicide is a possibility in any depressive illness, patients should not have access to large quantities of the drug. Hospitalize as soon as possible any patient suspected of having taken an overdose.

once a day at bedtime

Please see addendum on following page for other details of dosage and administration including divided daily doses, dosage in hospitalized patients, and dosage in elderly and adolescent patients.

TABLETS: 10 mg, 25 mg, and 50 mg INJECTION: 10 mg per ml

ELAVIL®

(AMITRIPTYLINE HCl | MSD)

MSD
MERCK SHARP & DOHME

For a brief summary of prescribing information, please see following page.

ELAVIL®
(AMITRIPTYLINE HCl | MSD)

added dosage versatility in clinically significant depression

Contraindications: Known hypersensitivity. Should not be given concomitantly with a monoamine oxidase inhibitor or within at least 14 days following the discontinuance of a monoamine oxidase inhibitor since hyperpyretic crises, severe convulsions, and deaths have occurred. When used to replace a monoamine oxidase inhibitor, initiate dosage of amitriptyline HCl cautiously with gradual increase in dosage until optimum response is achieved. Not recommended during the acute recovery phase following myocardial infarction.

Warnings: May block the antihypertensive action of guanethidine or similarly acting compounds. Should be used with caution in patients with a history of seizures or urinary retention, or with angle-closure glaucoma or increased intraocular pressure; in patients with angle-closure glaucoma, even average doses may precipitate an attack. Patients with cardiovascular disorders should be watched closely; arrhythmias, sinus tachycardia, and prolongation of the conduction time have been reported, particularly with high doses; myocardial infarction and stroke have been reported with drugs of this class. Close supervision is required for hyperthyroid patients or those receiving thyroid medication. May impair mental and/or physical abilities required for performance of hazardous tasks, such as operating machinery or driving a motor vehicle. Safe use during pregnancy and lactation has not been established; in pregnant patients, nursing mothers, or women who may become pregnant, weigh possible benefits against possible hazards to mother and child. Not recommended for patients under 12 years of age.

Precautions: Schizophrenic patients may develop increased symptoms of psychosis; patients with paranoid symptomatology may have an exaggeration of such symptoms; manic depressive patients may experience a shift to the manic phase. In these circumstances, the dose of amitriptyline HCl may be reduced or a major tranquilizer, such as perphenazine, may be administered concurrently.

When given with anticholinergic agents or sympathomimetic drugs, including epinephrine combined with local anesthetics, close supervision and careful adjustment of dosages are required. Use cautiously in patients receiving large doses of ethchlorvynol, since transient delirium has been reported on concurrent administration. May enhance the response to alcohol and the effects of barbiturates and other CNS depressants. The possibility of suicide in depressed patients remains during treatment and until significant remission occurs; this type of patient should not have easy access to large quantities of the drug. Concurrent electroshock therapy may increase the hazards associated with such therapy; such treatment should be limited to patients for whom it is essential. When possible, discontinue the drug several days before elective surgery. Both elevation and lowering of blood sugar levels have been reported.

Adverse Reactions: *Note:* Included in this listing are a few adverse reactions not reported with this specific drug. However, pharmacological similarities among the tricyclic antidepressant drugs require that each reaction be considered when amitriptyline is administered. *Cardiovascular:* Hypotension, hypertension, tachycardia, palpitation, myocardial infarction, arrhythmias, heart block, stroke. *CNS and Neuromuscular:* Confusional states; disturbed concentration; disorientation; delusions; hallucinations; excitement; anxiety; restlessness; insomnia; nightmares; numbness, tingling, and paresthesias of the extremities; peripheral neuropathy; incoordination; ataxia; tremors; seizures; alteration in EEG patterns; extrapyramidal symptoms; tinnitus. *Anticholinergic:* Dry mouth, blurred vision, disturbance of accommodation, constipation, paralytic ileus, urinary retention, dilatation of urinary tract. *Allergic:* Skin rash, urticaria, photosensitization, edema of face and tongue. *Hematologic:* Bone marrow depression including agranulocytosis, leukopenia, eosinophilia, purpura, thrombocytopenia. *Gastrointestinal:* Nausea, epigastric distress, vomiting, anorexia, stomatitis, peculiar taste, diarrhea, parotid swelling, black tongue. *Endocrine:* Testicular swelling and gynecomastia in the male, breast enlargement and galactorrhea in the female, increased or decreased libido, elevation and lowering of blood sugar levels. *Other:* Dizziness, weakness, fatigue, headache, weight gain or loss, increased perspiration, urinary frequency, mydriasis, drowsiness, jaundice, alopecia. *Withdrawal Symptoms:* Abrupt cessation of treatment after prolonged administration may produce nausea, headache, and malaise; these are not indicative of addiction.

Overdosage: Hospitalize as soon as possible all patients suspected of having taken an overdose. Treatment is symptomatic and supportive. In addition, the intravenous administration of 1 to 3 mg physostigmine salicylate has been reported to reverse the symptoms of tricyclic antidepressant poisoning.

How Supplied: Tablets containing 10 mg and 25 mg amitriptyline HCl, in single-unit packages of 100 and bottles of 100, 1000, and 5000; tablets containing 50 mg amitriptyline HCl, in single-unit packages of 100 and bottles of 100 and 1000; for intramuscular use, in 10-ml vials containing per ml: 10 mg amitriptyline HCl, 44 mg dextrose, 1.5 mg methylparaben and 0.2 mg propylparaben as preservatives, and water for injection q.s. 1 ml.

For more detailed information, consult your MSD representative or see full prescribing information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, Pa. 19486

addendum

MSD MERCK SHARP & DOHME

ELAVIL®
(AMITRIPTYLINE HCl | MSD)

dosage forms for differing patient needs

25 mg (yellow)

This tablet may prove useful for initial therapy in adult outpatients. Starting dosage is usually 75 mg daily in divided doses or 50 to 100 mg once a day at bedtime. If necessary, this dosage may be increased gradually to a total of 150 mg a day. When doses are divided, dosage increases are made preferably in the late afternoon or at bedtime. A sedative effect may be apparent before the antidepressant effect is noted. An adequate therapeutic effect may take as long as 30 days to develop.

50 mg (beige)

The 50-mg tablet may be advantageous whenever higher dosages are required, or when the single daily dose is given at bedtime. The 50-mg tablet may also be convenient for many hospitalized patients who may need 100 mg a day initially. In these patients, dosage may be increased gradually to 200 mg a day if necessary. A small number of hospitalized patients may need as much as 300 mg a day.

10 mg (blue)

Because lower doses are generally recommended for adolescents and elderly patients, the 10-mg tablets may be most serviceable. Ten mg three times a day with 20 mg at bedtime may be satisfactory in adolescent and elderly patients who do not tolerate higher doses.

INJECTION
10 mg per ml

For patients unable or unwilling to take tablets, the injectable form may be suitable initially. The tablets should replace the injection as soon as possible. Initial intramuscular dosage is 20 to 30 mg (2 to 3 ml) four times a day. When Injection ELAVIL is administered intramuscularly, the effects may appear more rapidly than with oral administration.

Usage in Children: In view of the lack of experience in children, this drug is not recommended at the present time for patients under 12 years of age.

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"May I propose a toast?"

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Donnagel with paregoric equivalent

Each 30 cc contains:

Kaolin	6.0 g
Pectin	142.8 mg
Hyoscyamine sulfate	0.1037 mg
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(equivalent to paregoric 6 ml.) (warning: may be habit forming.)	
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A·H·ROBINS

IN COUGHS OF COLDS, 'FLU, AND U.R.I.: CLEAR THE TRACT WITH THE ROBITUSSIN® LINE

Fall and winter coughs are back. Time to help clear the lower respiratory tract with the five Robitussins and Cough Calmers. All contain glyceryl guaiacolate, the efficient expectorant that works systemically to help increase the output of lower respiratory tract fluid. The enhanced flow of less viscid secretions soothes the tracheobronchial mucosa, promotes ciliary action, and makes thick, inspissated mucus less viscid and easier to raise. Available on your prescription or recommendation.

For unproductive coughs

ROBITUSSIN®

Each 5 cc. contains:
Glyceryl guaiacolate ..... 100 mg.
Alcohol, 3.5%

For severe coughs

ROBITUSSIN A-C® ℃

Each 5 cc. contains:
Glyceryl guaiacolate ..... 100 mg.
Codeine phosphate ..... 10.0 mg.
(warning: may be habit forming)
Alcohol, 3.5%

Non-narcotic for 6-8 hr. cough control

ROBITUSSIN-DM®

Each 5 cc. contains:
Glyceryl guaiacolate ..... 100 mg.
Dextromethorphan hydrobromide ..... 15 mg.
Alcohol, 1.4%

Robitussin-DM in solid form for "coughs on the go"

COUGH CALMERS®

Each Cough Calmer contains:
Glyceryl guaiacolate ..... 50 mg.
Dextromethorphan hydrobromide ..... 7.5 mg.

Clears nasal and sinus passages as it relieves coughs

ROBITUSSIN-PE®

Each 5 cc. contains:
Glyceryl guaiacolate ..... 100 mg.
Phenylephrine hydrochloride ..... 10 mg.
Alcohol, 1.4%

MEET THE NEWEST MEMBER OF THE LINE

Comprehensive decongestant action helps control cough and clear stuffy nose and sinuses. Non-narcotic.

ROBITUSSIN®-CF

Each 5 cc. contains:
Glyceryl guaiacolate ..... 50 mg.
Dextromethorphan hydrobromide ..... 10.0 mg.
Phenylpropanolamine hydrochloride ..... 12.5 mg.
Alcohol, 1.4%

Select the Robitussin® formulation that treats your patient's individual coughing needs:	Expectorant-Demulcent	Cough Suppressant	Long-Acting (6-8 hours)	Nasal Sinus Decongestant	Non-Narcotic
ROBITUSSIN®	●				●
ROBITUSSIN A-C®	●	●			
ROBITUSSIN-DM®	●	●	●		●
ROBITUSSIN-PE®	●			●	●
ROBITUSSIN®-CF	●	●		●	●
COUGH CALMERS®	■	■	■		■

A. H. Robins Company, Richmond, Va. 23220

THE NATURAL WAY

For more than thirty years PREMARIN (Conjugated Estrogens Tablets, U.S.P.) has been prepared with natural equine estrogens exclusively—without synthetic estrogen supplements. For more than thirty years it has provided the complete estrogen complex in the proportions found in its natural source. And for more than thirty years PREMARIN has enjoyed an unparalleled record of clinical efficacy and acceptance.

PREMARIN. The only estrogen preparation available that contains natural estrogens exclusively and also meets all U.S.P. specifications for conjugated estrogens. Assurance of quality for you and your patients.

PREMARIN . . . naturally.

BRIEF SUMMARY
(For full prescribing information, see package circular.)
PREMARIN®
(Conjugated Estrogens Tablets, U.S.P.)

Indications: Based on a review of PREMARIN Tablets by the National Academy of Sciences-National Research Council and/or other information, FDA has classified the indications for use as follows:
Effective: As replacement therapy for naturally occurring or surgically induced estrogen deficiency states associated with: the climacteric, including the menopausal syndrome and postmenopause; senile vaginitis and kraurosis vulvae, with or without pruritus.
"Probably" effective: For estrogen deficiency-induced osteoporosis, and only when used in conjunction with other important therapeutic measures such as diet, calcium, physiotherapy, and good general health-promoting measures. Final classification of this indication requires further investigation.

Contraindications: Short acting estrogens are contraindicated in patients with (1) markedly impaired liver function; (2) known or suspected carcinoma of the breast, except those cases of progressing disease not amenable to surgery or irradiation occurring in women who are at least 5 years postmenopausal; (3) known or suspected estrogen-dependent neoplasia, such as carcinoma of the endometrium; (4) thromboembolic disorders, thrombophlebitis, cerebral embolism, or in patients with a past history of these conditions; (5) undiagnosed abnormal genital bleeding.
Warnings: Estrogen therapy should not be given to women with recurrent chronic mastitis or abnormal mammograms except, if in the opinion of the physician, it is warranted despite the possibility of aggravation of the mastitis or stimulation of undiagnosed estrogen-dependent neoplasia.

The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, retinal thrombosis, cerebral embolism and pulmonary embolism). If these occur or are suspected, estrogen therapy should be discontinued immediately.

Estrogens may be excreted in the mother's milk and an estrogenic effect upon the infant has been described. The long range effect on the nursing infant cannot be determined at this time.

Hypercalcemia may occur in as many as 15 percent of breast cancer patients with metastases, and this usually indicates progression of bone metastases. This occurrence depends neither on dose nor on immobilization. In the presence of progression of the cancer or hypercalcemia, estrogen administration should be stopped.

A statistically significant association has been reported between maternal ingestion of diethylstilbestrol during pregnancy and the occurrence of vaginal carcinoma in the offspring. This occurred with the use of diethylstilbestrol for the treatment of threatened abortion or high risk pregnancies. Whether or not such an association is applicable to all estrogens is not known at this time. In view of this finding, however, the use of any estrogen in pregnancy is not recommended.

Failure to control abnormal uterine bleeding or unexpected recurrence is an indication for curettage.
Precautions: As with all short acting estrogens, the following precautions should be observed:

A complete pretreatment physical examination should be performed with special reference to pelvic and breast examinations.

To avoid prolonged stimulation of the endometrium and breasts in climacteric or hypogonadal women, estrogens should be administered cyclically (3 week regimen with 1 week rest period—withdrawal bleeding may occur during rest period).

Because of individual variation in endogenous estrogen production, relative overdosage may occur which could cause undesirable effects such as abnormal or excessive uterine bleeding, mastodynia and edema.

Because of salt and water retention associated with estrogenic anabolic activity, estrogens should be used with caution in patients with epilepsy, migraine, asthma, cardiac, or renal disease.

If unexplained or excessive vaginal bleeding should occur, reexamination should be made for organic pathology.

Pre-existing uterine fibromyomata may increase in size while using estrogens; therefore, patients should be examined at regular intervals while receiving estrogenic therapy.

The pathologist should be advised of estrogen therapy when relevant specimens are submitted.

Because of their effects on epiphyseal closure, estrogens should be used judiciously in young patients in whom bone growth is incomplete.

Prolonged high dosages of estrogens will inhibit anterior pituitary functions. This should be borne in mind when treating patients in whom fertility is desired.

The age of the patient constitutes no absolute limiting factor, although treatment with estrogens may mask the onset of the climacteric.

Certain liver and endocrine function tests may be affected by exogenous estrogen administration. If test results are abnormal in a patient taking estrogen, they should be repeated after estrogen has been withdrawn for one cycle.
Adverse Reactions: The following adverse reactions have been reported associated with short acting estrogen administration:
nausea, vomiting, anorexia
gastrointestinal symptoms such as abdominal cramps and bloating
breakthrough bleeding, spotting, unusually heavy withdrawal bleeding (See DOSAGE AND ADMINISTRATION)
breast tenderness and enlargement
reactivation of endometriosis
possible diminution of lactation when given immediately postpartum
loss of libido and gynecomastia in males
edema
aggravation of migraine headaches
change in body weight (increase, decrease)
headache
allergic rash
hepatic cutaneous porphyria becoming manifest
Dosage and Administration: PREMARIN should be administered cyclically (3 weeks of daily estrogen and 1 week off) for all indications except selected cases of carcinoma and prevention of postpartum breast engorgement.

Menopausal Syndrome—1.25 mg. daily, cyclically. Adjust dosage upward or downward according to severity of symptoms and response of the patient. For maintenance, adjust dosage to lowest level that will provide effective control.

If the patient has not menstruated within the last two months or more, cyclic administration is started arbitrarily. If the patient is menstruating, cyclic administration is started on day 5 of bleeding. If breakthrough bleeding (bleeding or spotting during estrogen therapy) occurs, increase estrogen dosage as needed to stop bleeding. In the following cycle, employ the dosage level used to stop breakthrough bleeding in the previous cycle. In subsequent cycles, the estrogen dosage is gradually reduced to the lowest level which will maintain the patient symptom-free.

Postmenopause—as a protective measure against estrogen deficiency-induced degenerative changes (*e.g.* osteoporosis, atrophic vaginitis, kraurosis vulvae)—0.3 mg. to 1.25 mg. daily and cyclically. Adjust dosage to lowest effective level.

Osteoporosis (to retard progression)—usual dosage 1.25 mg. daily and cyclically.

Senile Vaginitis, Kraurosis Vulvae with or without Pruritus—0.3 mg. to 1.25 mg. or more daily, depending upon the tissue response of the individual patient. Administer cyclically.
How Supplied: PREMARIN (Conjugated Estrogens Tablets, U.S.P.)

No. 865—Each *purple* tablet contains 2.5 mg., in bottles of 100 and 1,000.

No. 866—Each *yellow* tablet contains 1.25 mg., in bottles of 100 and 1,000. Also in unit dose package of 100.

No. 867—Each *red* tablet contains 0.625 mg., in bottles of 100 and 1,000.

No. 868—Each *green* tablet contains 0.3 mg., in bottles of 100 and 1,000. 7352

PREMARIN®

BRAND OF **CONJUGATED ESTROGENS TABLETS, U.S.P.**

CONTAINS ONLY NATURAL ESTROGENS ...NO SYNTHETICS OR SUPPLEMENTS

Ayerst.

AYERST LABORATORIES
New York, N.Y. 10017

When low back pain* interferes...
Help relieve pain, restore mobility with
PARAFON FORTE® Tablets
chlorzoxazone † 250 mg.; acetaminophen 300 mg.
*This drug has been evaluated as "probably" effective for this indication.
See brief summary of prescribing information on facing page for Indications, Contraindications, Warnings, Precautions and Adverse Reactions.
©McN 74

PARAFON FORTE® tablets help relieve pain, restore mobility and stop pain-spasm feedback by providing:

a nonsalicylate analgesic equal to aspirin for relief of pain,[1,2] yet unlikely to cause the gastric irritation,[2,3] allergic reactions[2] or increased bleeding time[4] associated with aspirin therapy...

and a skeletal muscle relaxant shown in extensive clinical studies to afford relief of discomfort in acute musculoskeletal conditions*[5-7] but which is not an antihistamine or tranquilizer derivative and is unlikely to produce a tranquilizing or sedative effect.[5,7,8]

* **Indications:** Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows: "Probably" effective as an adjunct to rest and physical therapy for the relief of discomfort associated with acute, painful musculoskeletal conditions. The mode of action of this drug has not been clearly identified, but may be related to its sedative properties. Chlorzoxazone does not directly relax tense skeletal muscles in man.

Contraindications: Sensitivity to either component.
Warnings: *Usage in Pregnancy*—Use in women of childbearing potential only when potential benefits outweigh possible risks.
Precautions: Exercise caution in patients with known allergies or history of drug allergies. If a sensitivity reaction or any signs or symptoms suggestive of liver dysfunction are observed, the drug should be stopped.
Adverse Reactions: Occasionally, drowsiness, dizziness, lightheadedness, malaise, overstimulation or gastrointestinal disturbances may be noted; rarely, allergic-type skin rashes, petechiae, ecchymoses, angioneurotic edema or anaphylactic reactions. In rare instances, chlorzoxazone may possibly have been associated with gastrointestinal bleeding. While PARAFLEX® (chlorzoxazone) tablets and other chlorzoxazone-containing products have been suspected as being the cause of hepatic toxicity in approximately twenty-four patients, it was not possible to state that the dysfunction was or was not drug induced.
Usual Adult Dosage: Two tablets q.i.d.
Supplied: Scored, light green tablets, imprinted "McNEIL"—bottles of 100.

References: **1.** Batterman, R.C., and Grossman, A.J.: Fed. Proc. *14*:316, 1955. **2.** Goodman, L.S., and Gilman, A., ed.: The Pharmacological Basis of Therapeutics, ed. 4. New York, The Macmillan Company, 1970. **3.** Vickers, F.N.: Gastroint. Endosc. *14*:94, 1967. **4.** Mielke, C.H., Jr., and Britten, A.F.H.: New Engl. J. Med. *282*:1270, 1970 (Corresp.). **5.** Vernon, W.G.: Curr. Therap. Res. *14*:801, 1972. **6.** Scheiner, J.J.: Curr. Therap. Res. *14*:168, 1972. **7.** Walker, J.M.: Curr. Therap. Res. *15*:248, 1973. **8.** Data on file, McNeil Laboratories, Inc.

† U.S. Patent No. 2,895,877

McNEIL McNeil Laboratories, Inc.
Fort Washington, Pa. 19034

BOOKS RECEIVED

Books received by THE WESTERN JOURNAL OF MEDICINE *are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.*

HANDBOOK OF MEDICAL TREATMENT—Fourteenth Edition—Milton J. Chatton, MD, Clinical Associate Professor of Medicine, Stanford University School of Medicine, Senior Attending Physician, Santa Clara Valley Medical Center, San Jose, and Research Associate, Palo Alto Medical Research Foundation. Lange Medical Publications, Drawer L, Los Altos, CA (94022), 1974. 640 pages, $7.50.

HANDBOOK OF OBSTETRICS & GYNECOLOGY—Fifth Edition—Ralph C. Benson, MD, Professor of Obstetrics and Gynecology and Chairman, Department of Obstetrics and Gynecology, University of Oregon Medical School Hospitals and Clinics, Portland. Lange Medical Publications, Drawer L, Los Altos, CA (94022), 1974. 770 pages, $8.00.

THE HEMORRHAGIC DISEASES AND THE PATHOLOGY OF HEMOSTASIS—Armand J. Quick, PhD, MD, Research Professor, Hemostasis Research Laboratory, Medical College of Wisconsin, Milwaukee. Charles C Thomas, Publisher, 301-327 Lawrence Avenue, Springfield IL (62703), 1974. 380 pages, $23.75.

HEROIN ADDICTION IN BRITAIN—What Americans Can Learn from the English Experience—Horace Freeland Judson. Harcourt Brace Jovanovich, Inc., 757 Third Avenue, New York City (10017), 1974. 200 pages, $6.95.

INTENSIVE CARE—Aake Waahlin, Lars Westermark, Ansje van der Vliet, Central Anesthesiological Department, Karolinska Sjukhuset, Stockholm. John Wiley & Sons, Inc., Publishers, 605 Third Avenue, New York City (10016), 1974. 323 pages, $20.00.

MICROBIOLOGY OF HUMAN SKIN—Volume 2 in the Series: Major Problems in Dermatology—W. C. Noble, PhD, MRC Path, Senior Lecturer, Institute of Dermatology, Head of Department of Bacteriology, St. John's Hospital for Diseases of the Skin, London; and Dorothy A. Somerville, PhD, Lecturer, Department of Bacteriology, University of Glasgow, Royal Infirmary, Glasgow. W. B. Saunders Company, West Washington Square, Philadelphia (19105), 1974. 341 pages, $22.50.

PRIMARY CARE: WHERE MEDICINE FAILS—Edited by Spyros Andreopoulos, Information Officer, Stanford University Medical Center and Editor of **Stanford M.D.** John Wiley & Sons, Inc., Publishers, 605 Third Avenue, New York City (10016), 1974. 212 pages, $9.95.

PSYCHIATRY IN PRIMARY CARE—Remi J. Cadoret, MD, Professor of Psychiatry, Departments of Psychiatry and Family Practice, School of Medicine, University of Iowa; and Lucy J. King, MD, Associate Professor, Department of Psychiatry, School of Medicine, Washington University, St. Louis. The C. V. Mosby Company, Publishers, 3301 Washington Boulevard, St. Louis, MO (63103), 1974. 339 pages, $12.95.

REVIEW OF MEDICAL PHARMACOLOGY—4th Edition—Frederick H. Meyers, MD, Professor of Pharmacology; Ernest Jawetz, PhD, MD, Professor and Chairman, Department of Microbiology, Professor of Medicine, Lecturer in Pediatrics; and Alan Goldfien, MD, Professor of Medicine, Departments of Medicine and Obstetrics & Gynecology and Cardiovascular Research Institute, University of California, San Francisco. Lange Medical Publications, Drawer L, Los Altos, CA (94022), 1974. 721 pages, $10.50.

SYMPOSIUM ON MANAGEMENT OF CLEFT LIP AND PALATE AND ASSOCIATED DEFORMITIES—Proceedings of the Symposium of the Educational Foundation of the American Society of Plastic and Reconstructive Surgeons—Volume 8—Edited by Nicholas G. Georgiade, DDS, MD, FACS, Professor of Plastic Maxillofacial and Oral Surgery, Duke University Medical School, Durham; and contributing editor Robert F. Hagerty, MD, FACS, Director, Saul Alexander Cleft Lip and Palate Center, and Clinical Associate Professor of Surgery (Plastic), Medical University of South Carolina, Charleston. The C. V. Mosby Company, 3301 Washington Blvd., St. Louis, MO (63103), 1974. 324 pages, $42.50.

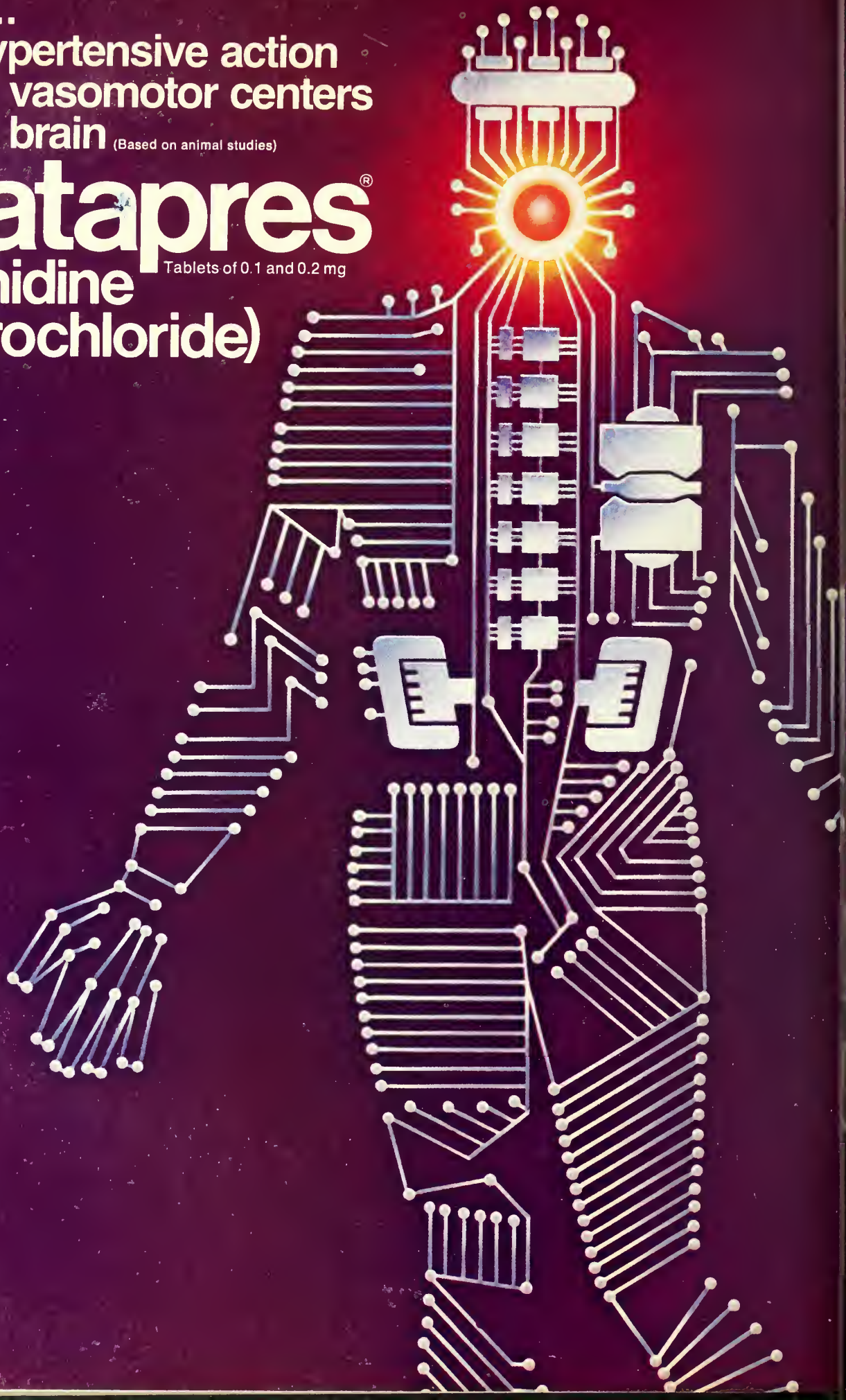
SYMPOSIUM ON RECONSTRUCTION OF THE AURICLE—Proceedings of the Symposium of the Educational Foundation of the American Society of Plastic and Reconstructive Surgeons—Volume 10—Edited by Radford C. Tanzer, MD, Clinical Professor of Plastic Surgery, Emeritus, Dartmouth Medical School, Hanover; Consultant in Plastic Surgery, Veterans Administration Hospital, White River Junction, Vermont; and Milton T. Edgerton, MD, Professor and Chairman, Department of Plastic Surgery, University of Virginia School of Medicine, Charlottesville. The C. V. Mosby Company, Ltd., Publishers, 86 Northline Rd., Toronto, Ontario M4B 3E5, 1974. 312 pages, $42.50.

WELFARE MEDICINE IN AMERICA—A Case Study of Medicaid—Robert Stevens, Professor of Law, Yale University; and Rosemary Stevens, Associate Professor of Public Health, Yale University. The Free Press, A Division of Macmillan Publishing Co., Inc., 866 Third Ave., New York City (10022), 1974. 386 pages, $13.95.

Now...
antihypertensive action
at the vasomotor centers
in the brain (Based on animal studies)

Catapres®
(clonidine hydrochloride)

Tablets of 0.1 and 0.2 mg



Central action

Catapres appears to lower blood pressure through central alpha-adrenergic stimulation, as shown in animal studies. This results in diminution—but not blocking—of sympathetic outflow from cardioaccelerator and vasoconstrictor centers in the medulla.

Not a "depleter", "blocker", "inhibitor" or "false transmitter"

Not a rauwolfia

Effective in hypertension, mild to severe

Mild and infrequent orthostatic hypotension

Normal hemodynamic responses to exercise are unaffected

Renal blood flow and glomerular filtration rate essentially unchanged

Mild to moderate potency

The most common side effects are dry mouth, drowsiness and sedation. These generally tend to diminish with continued therapy. Other potential adverse reactions are listed in the Brief Summary.

Catapres® (clonidine hydrochloride)
Tablets of 0.1 mg and 0.2 mg

Indication: The drug is indicated in the treatment of hypertension. As an antihypertensive drug, Catapres (clonidine hydrochloride) is mild to moderate in potency. It may be employed in a general treatment program with a diuretic and/or other antihypertensive agents as needed for proper patient response.

Warnings: Tolerance may develop in some patients necessitating a reevaluation of therapy.
Usage in Pregnancy: In view of embryotoxic findings in animals, and since information on possible adverse effects in pregnant women is limited to uncontrolled clinical data, the drug is not recommended in women who are or may become pregnant unless the potential benefits outweigh the potential risk to mother and fetus.
Usage in Children: No clinical experience is available with the use of Catapres (clonidine hydrochloride) in children.

Precautions: When discontinuing Catapres (clonidine hydrochloride), reduce the dose gradually over 2 to 4 days to avoid a possible rapid rise in blood pressure and associated subjective symptoms such as nervousness, agitation, and headache. Patients should be instructed not to discontinue therapy without consulting their physician. Rare instances of hypertensive encephalopathy and death have been recorded after cessation of clonidine hydrochloride therapy. A causal relationship has not been established in these cases. It has been demonstrated that an excessive rise in blood pressure, should it occur, can be reversed by resumption of clonidine hydrochloride therapy or by intravenous phentolamine. Patients who engage in potentially hazardous activities, such as operating machinery or driving should be advised of the sedative effect. This drug may enhance the CNS-depressive effects of alcohol, barbiturates and other sedatives. Like any other agent lowering blood pressure, clonidine hydrochloride should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease or chronic renal failure.

As an integral part of their overall long-term care, patients treated with Catapres (clonidine hydrochloride) should receive periodic eye examinations. While, except for some dryness of the eyes, no drug-related abnormal ophthalmologic findings have been recorded with Catapres, in several studies the drug produced a dose-dependent increase in the incidence and severity of spontaneously occurring retinal degeneration in albino rats treated for 6 months or longer.

Adverse Reactions: The most common reactions are dry mouth, drowsiness and sedation. Constipation, dizziness, headache, and fatigue have been reported. Generally these effects tend to diminish with continued therapy. The following reactions have been associated with the drug, some of them rarely. (In some instances an exact causal relationship has not been established). These include: Anorexia, malaise, nausea, vomiting, parotid pain, mild transient abnormalities in liver function tests; one report of possible drug-induced hepatitis without icterus and hyperbilirubinemia in a patient receiving clonidine hydrochloride, chlorthalidone and papaverine hydrochloride.

Weight gain, transient elevation of blood glucose, or serum creatine phosphokinase; congestive heart failure, Raynaud's phenomenon; vivid dreams or nightmares, insomnia, other behavioral changes, nervousness, restlessness, anxiety and mental depression. Also rash, angioneurotic edema, hives, urticaria, thinning of the hair, pruritus not associated with a rash, impotence, urinary retention, increased sensitivity to alcohol, dryness, itching or burning of the eyes, dryness of the nasal mucosa, pallor, gynecomastia, weakly positive Coombs' test, asymptomatic electrocardiographic abnormalities manifested as Wenckebach period or ventricular trigeminy.

Overdosage: Profound hypotension, weakness, somnolence, diminished or absent reflexes and vomiting followed the accidental ingestion of Catapres (clonidine hydrochloride) by several children from 19 months to 5 years of age. Gastric lavage and administration of an analeptic and vasopressor led to complete recovery within 24 hours. Tolazoline in intravenous doses of 10 mg at 30-minute intervals usually abolishes all effects of Catapres (clonidine hydrochloride) overdosage.

How Supplied: Catapres, brand of clonidine hydrochloride, is available as 0.1 mg (tan) and 0.2 mg (orange) oval, single-scored tablets in bottles of 100.

For complete details, please see full prescribing information.

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Boehringer Ingelheim GmbH

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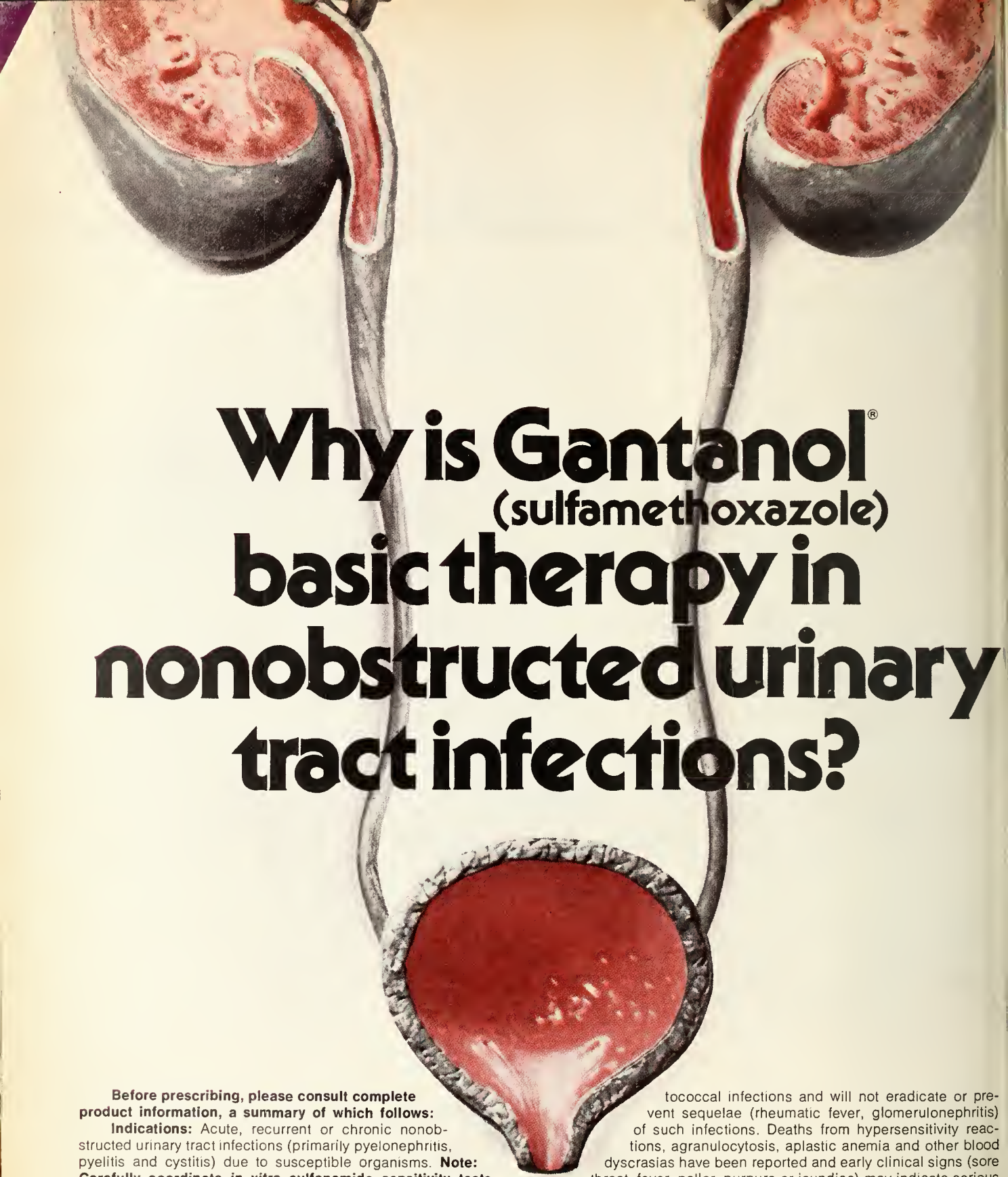
Boehringer Ingelheim

Boehringer Ingelheim Ltd.
Elmsford, New York 10523



Why is Gantanol® (sulfamethoxazole) basic therapy in nonobstructed urinary tract infections?

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Acute, recurrent or chronic nonobstructed urinary tract infections (primarily pyelonephritis, pyelitis and cystitis) due to susceptible organisms. **Note: Carefully coordinate *in vitro* sulfonamide sensitivity tests with bacteriologic and clinical response; add aminobenzoic acid to follow-up culture media. The increasing frequency of resistant organisms limits the usefulness of antibacterials including sulfonamides, especially in chronic or recurrent urinary tract infections.** Measure sulfonamide blood levels as variations may occur; 20 mg/100 ml should be maximum total level.

Contraindications: Sulfonamide hypersensitivity; pregnancy at term and during nursing period; infants less than two months of age.

Warnings: Safety during pregnancy has not been established. Sulfonamides should not be used for group A beta-hemolytic streptococcal infections and will not eradicate or prevent sequelae (rheumatic fever, glomerulonephritis) of such infections. Deaths from hypersensitivity reactions, agranulocytosis, aplastic anemia and other blood dyscrasias have been reported and early clinical signs (sore throat, fever, pallor, purpura or jaundice) may indicate serious blood disorders. Frequent CBC and urinalysis with microscopic examination are recommended during sulfonamide therapy. Insufficient data on children under six with chronic renal disease.

Precautions: Use cautiously in patients with impaired renal or hepatic function, severe allergy, bronchial asthma; in glucose-6-phosphate dehydrogenase-deficient individuals in whom dose-related hemolysis may occur. Maintain adequate fluid intake to prevent crystalluria and stone formation.

Adverse Reactions: *Blood dyscrasias* (agranulocytosis, aplastic anemia, thrombocytopenia, leukopenia, hemolytic anemia, pur-

Because it is considered a good choice...

- for efficacy in nonobstructed cystitis, pyelonephritis and pyelitis
- for control of susceptible *E. coli, Klebsiella-Aerobacter, Staph. aureus, Proteus mirabilis* and, less frequently, *Proteus vulgaris*
- for prompt antibacterial blood and urine levels in from 2 to 3 hours after initial 2-gram adult dose
- for economical around-the-clock coverage
- for maximum patient cooperation with easy-to-remember B.I.D. dosage

Basic Therapy

Gantanol®

(sulfamethoxazole)

Tablets/Suspension
(0.5 Gm) (0.5 Gm/teasp.)

pura, hypoprothrombinemia and methemoglobinemia); *allergic reactions* (erythema multiforme, skin eruptions, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis); *gastrointestinal reactions* (nausea, emesis, abdominal pains, hepatitis, diarrhea, anorexia, pancreatitis and stomatitis); *CNS reactions* (headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo and insomnia); *miscellaneous reactions* (drug fever, chills, toxic nephrosis with oliguria and anuria, periarteritis nodosa and L.E. phenomenon). Due to certain chemical similarities with some goitrogens, diuretics (acetazolamide, thiazides) and oral hypoglycemic agents, sulfonamides have caused rare instances of goiter production, diuresis and hypoglycemia as well as thyroid malignancies in rats following long-term administration. Cross-sensitivity with these agents may exist.

Dosage: Systemic sulfonamides are contraindicated in infants under 2 months of age (except adjunctively with pyrimethamine in congenital toxoplasmosis).

Usual adult dosage: 2 Gm (4 tabs or teasp.) initially, then 1 Gm *b.i.d.* or *t.i.d.* depending on severity of infection.

Usual child's dosage: 0.5 Gm (1 tab or teasp.)/20 lbs of body weight initially, then 0.25 Gm/20 lbs *b.i.d.* Maximum dose should not exceed 75 mg/kg/24 hrs.

Supplied: Tablets, 0.5 Gm sulfamethoxazole; Suspension, 0.5 Gm sulfamethoxazole/teaspoonful.

ROCHE

Roche Laboratories
Division of Hoffmann-La Roche Inc.
Nutley, N.J. 07110

Today's woman doesn't want to
spend a lot of time searching for a
contraceptive she's comfortable with.

Neither do you.

If adverse reactions such as spotting r breakthrough bleeding occur when she arts on an oral contraceptive, you're mong the first to hear about it. Anxious, orried, she's in your office immediately. Or n the phone, at all hours.

Ovral® helps eliminate questions.

To help her maintain her busy schedule –and not interfere with yours—you might consider starting her on Ovral. Experience has shown that most patients who start on Ovral stay on Ovral. Its low incidence of spotting, breakthrough bleeding and other common adverse reactions undoubtedly contributes to this fine record.*

Balanced hormone content.

To achieve an optimum dose, Ovral combines one-half milligram of norgestrel, a totally synthetic progestational agent, and 50 micrograms of ethinyl estradiol.

"Normal" periods, few drop-outs.

You know how important a "normal" period is to a woman on an oral contraceptive. With Ovral, duration of cycle, length of period and amount of flow usually resemble those of normal periods. This is one reason why the drop-out rate for Ovral is low—4.5% in clinical trials totaling 127,872 cycles.

Today's woman tends to stay on Ovral. She's seldom in your office or on the phone with questions or complaints.

Ovral.® A very "quiet" pill.

*Serious as well as minor adverse reactions have been reported following the use of all oral contraceptives. The physician should remain alert to their earliest manifestations and in the event of serious adverse reactions should avoid any oral contraceptives. Special note, contraindications, warnings, precautions, and adverse reactions in the accompanying IN BRIEF should be carefully considered.

OVRAL®

Each tablet contains 0.5 mg. norgestrel with 0.05 mg. ethinyl estradiol.

Wyeth Laboratories
Philadelphia, Pa. 19101

Important information on next page.

Ovral.® A very "quiet" pill.

IN BRIEF.

SPECIAL NOTE: Oral contraceptives have been marketed in the United States since 1960. Reported pregnancy rates vary from product to product. The effectiveness of the sequential products appears to be somewhat lower than that of the combination products. Both types provide almost completely effective contraception.

An increased risk of thrombaembolic disease associated with the use of hormonal contraceptives has now been shown in studies conducted in both Great Britain and the United States. Other risks, such as those of elevated blood pressure, liver disease and reduced tolerance to carbohydrates, have not been quantitated with precision.

Long-term administration of both natural and synthetic estrogens in subprimate animal species in multiples of the human dose increases the frequency for some animal carcinomas. These data cannot be transposed directly to man. The possible carcinogenicity due to the estrogens can neither be affirmed nor refuted at this time. Close clinical surveillance of all women taking oral contraceptives must be continued.

INDICATIONS: For oral contraception.

CONTRAINDICATIONS: 1. Thrombophlebitis, thromboembolic disorders, cerebral apoplexy, or a past history of these conditions; 2. Markedly impaired liver function; 3. Known or suspected carcinoma of the breast, 4. Known or suspected estrogen dependent neoplasia. 5. Undiagnosed abnormal genital bleeding

WARNINGS: 1. The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism, and retinal thrombosis). Should any of these occur or be suspected, the drug should be discontinued immediately.

Retrospective studies of morbidity and mortality in Great Britain and studies of morbidity in the United States have shown a statistically significant association between thrombophlebitis, pulmonary embolism, and cerebral thrombosis and embolism and the use of oral contraceptives. There have been three principal studies in Britain[1-3] leading to this conclusion, and one[4] in this country. The estimate of the relative risk of thromboembolism in the study by Vessey and Doll[3] was about sevenfold, while Sartwell and associates in the United States found a relative risk of 4.4, meaning that the users are several times as likely to undergo thromboembolic disease without evident cause as non-users. The American study also indicated that the risk did not persist after discontinuation of administration and that it was not enhanced by long continued administration. The American study was not designed to evaluate a difference between products. However, the study suggested that there might be an increased risk of thromboembolic disease in users of sequential products. This risk cannot be quantitated, and further studies to confirm this finding are desirable.

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2. Discontinue medication pending examination if there is sudden, partial or complete loss of vision, or if there is sudden onset of proptosis, diplopia, or migraine. If examination reveals papilledema or retinal vascular lesions, medication should be withdrawn. 3. Since the safety of Ovral in pregnancy has not been demonstrated, it is recommended that for any patient who has missed two consecutive periods, pregnancy should be ruled out before continuing the contraceptive regimen. If the patient has not adhered to prescribed schedule the possibility of pregnancy should be considered at the time of the first missed period. 4. A small fraction of the hormonal agents in oral contraceptives has been identified in the milk of mothers receiving these drugs. The long range effect to the nursing infant cannot be determined at this time.

PRECAUTIONS: 1. The pretreatment and periodic physical examinations should include special reference to breasts and pelvic organs, including Papanicolaou smear since estrogens have been known to produce tumors, some of them malignant, in five species of subprimate animals. 2. Endocrine and possibly liver-function tests may be affected by treatment with Ovral. Therefore, if such tests are abnormal in a patient taking Ovral, it is recommended that they be repeated after the drug has been withdrawn for two months. 3. Under the influence of estrogen-progestogen preparations, preexisting uterine fibromyomata may increase in size. 4. Because these agents may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, cardiac or renal dysfunction, require careful observation. 5. In breakthrough bleeding, and in all cases of irregular bleeding per vaginam, nonfunctional causes should be borne in mind. In undiagnosed bleeding per vaginam, adequate diagnostic measures are indicated. 6. Patients with a history of psychic depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree. 7. Any possible influence of prolonged Ovral therapy on pituitary, ovarian, adrenal, hepatic or uterine function awaits further study. 8. A decrease in glucose tolerance has been observed in a significant percentage of patients on oral contraceptives. The mechanism of this decrease is obscure. For this reason, diabetic patients should be carefully observed while receiving Ovral therapy. 9. The age of the patient constitutes no absolute limiting factor, although treatment with Ovral may mask the onset of the climacteric. 10. The pathologist should be advised of Ovral therapy when relevant specimens are submitted. 11. Susceptible women may experience an increase in blood pressure following administration of contraceptive steroids.

ADVERSE REACTIONS OBSERVED IN PATIENTS RECEIVING ORAL CONTRACEPTIVES: A statistically significant association has been demonstrated between use of oral contraceptives and the following serious adverse reactions: thrombophlebitis, pulmonary embolism, cerebral thrombosis.

Although available evidence is suggestive of an association, such a relationship has been neither confirmed nor refuted for the following serious adverse reactions: neuro-ocular lesions (e.g., retinal thrombosis and optic neuritis).

The following adverse reactions are known to occur in patients receiving oral contraceptives: nausea, vomiting, gastrointestinal symptoms (e.g., abdominal cramps and bloating), breakthrough bleeding, spotting, change in menstrual flow, amenorrhea during and after treatment, dysmenorrhea, edema, chloasma or melasma, breast changes (tenderness, discomfort, enlargement and secretion), change in weight (increase or decrease), changes in cervical erosion and cervical secretions, suppression of lactation when given immediately post-partum, cholestatic jaundice, migraine, acne, rash (allergic), hypertension, rise in blood pressure in susceptible individuals, mental depression, pain in legs, arms or body, paresthesias, allergy, palpitations, vasomotor symptoms, dyspnea, insomnia, blurred vision, chest pain, urinary tract symptoms, dyspareunia, neuralgia and myalgia, excess salivation, dryness of mouth, heartburn, minor eye problems.

Although the following adverse reactions have been reported in users of oral contraceptives, an association has been neither confirmed nor refuted: anovulation post-treatment, premenstrual-like syndrome, changes in libido, changes in appetite, cystitis-like syndrome, headache, nervousness, dizziness, fatigue, backache, hirsutism, loss of scalp hair, erythema multiforme, erythema nodosum, hemorrhagic eruption, and itching and vaginal discharge.

The following laboratory results may be altered by the use of oral contraceptives—hepatic function: increased sulfobromophthalein retention and other tests, coagulation tests: increase in prothrombin, Factors VII, VIII, IX and X; thyroid function: increase in PBI and butanol-extractable protein-bound iodine and decrease in T_3 uptake values; metyrapone test; and pregnanediol determination.

Note: For more specific details on Ovral, refer to package insert.

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Refer to: Allaire BI, Schroeder JS: Prinzmetal's angina—Clinical and anatomic aspects. West J Med 122:187-193, Mar 1975

Prinzmetal's Angina

Clinical and Anatomic Aspects

BASIL I. ALLAIRE, MD, *and* JOHN S. SCHROEDER, MD, *Stanford*

A review of 120 patients who had a discharge diagnosis of intermediate coronary syndrome showed 12 patients with documented transient ST elevation during spontaneous rest pain consistent with Prinzmetal's angina. Coronary arteriography showed severe proximal occlusive coronary atherosclerosis in nine of the patients, and normal or minimal disease in the other three patients. In two of these three, there was documented coronary arterial spasm with reproduction of symptoms during arteriography. Although a shorter history of chest pain, presence of an old myocardial infarction and a positive finding on electrocardiogram treadmill test tended to predict the patients with severe occlusive coronary artery disease, these methods were inadequate to select candidates for arteriography. All patients responded well to nitroglycerine while in the hospital. Five of the nine patients with coronary artery disease had coronary bypass operations, with two excellent, two fair and one poor result. One of the three patients with normal findings on coronary arteriograms died with refractory ventricular arrhythmia six months after study. The other two have had good-to-moderate relief of symptoms on long-acting vasodilators and propranolol. Current concepts of the syndrome of Prinzmetal's angina and ST elevation are reviewed. It appears that this syndrome has a wide spectrum of clinical presentations and coronary arteriographic anatomies.

In 1959, Prinzmetal and co-workers first described a variant form of angina, characterized by recurrent spontaneous episodes of chest pain associated with transient ST segment elevation during these episodes.[1] The pain frequently was of long duration and cyclical in nature. Postmortem examination in several of their patients showed severe proximal occlusive coronary artery disease. The authors postulated that the pain syndrome occurred during major vessel occlusion due to transient spasm. This theory was supported by experimental work showing ST elevation in electrocardiograms of dogs on occlusion near the origin of the coronary artery, with rapid resolution on release of the ligature.[2] These observations

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have been confirmed by other reports of severe proximal occlusive coronary artery disease on coronary arteriography in these patients.[2-4] Recently, reports from this institution and others have described normal or near-normal findings on coronary arteriograms in patients with a well-documented clinical syndrome of variant angina.[5,6] These reports have documented coronary spasm during the arteriogram and suggest that spasm causing near-occlusion of a normal or minimally diseased coronary artery may also be responsible for the syndrome of variant angina in some patients. This wide disparity of coronary arteriographic anatomy, with its significant implications for flexibility in the diagnosis and treatment, precipitated a retrospective review of patients with variant angina studied at Stanford University Hospital. The purpose of this report is to present our experience with the spectrum of clinical presentations, differing coronary arteriographic anatomies and the implications of these results regarding the pathophysiology of the rest angina and ST segment elevation and its treatment.

Methods

We reviewed the medical records of Stanford University Hospital from 1965 to 1973 and found that 120 patients had been discharged with diagnoses which included preinfarction angina, angina decubitus, coronary insufficiency, variant angina and Prinzmetal's angina. All these medical records were reviewed in detail. Twelve patients fulfilled the electrocardiographic criteria; that is, documented ST segment elevation recorded during chest pain in the hospital, with return to isoelectric line after subsidence of the pain. These episodes were not associated with significant serum glutamic-oxaloacetic transaminase (SGOT), lactic dehydrogenase (LDH) or creatine phosphokinase (CPK) enzyme rises and were not associated with the development of Q waves on serial electrocardiograms. In three patients, the ST elevation

TABLE 1.—*Patient Characteristics and Findings*

Patient	*Age (yrs)/ Sex*	*Duration of Symptoms*	*CAD Risk Factors*	*Results on Electrocardiography*	
				*Pain**	*Pain-free*
1	48/♂	2 years	FHx	ST elev. V_{1-3}	Normal
2	61/♀	3 years	↑lipids, obesity, smoking, HBP	ST elev. II, III, AVF, 1° A-V block	Normal
3	47/♂	1 week	FHx	ST elev. II, III, AVF, arrhythmias	Inferior MI
4	47/♀	5 years	↑lipids, smoking, HBP	ST elev. II, III, AVF	Normal
5	71/♀	1 month	↑lipids	ST elev. AVL, V_{1-4}	Deep inversion, T, V_1-V_4
6	49/♂	1 year	FHx, ↑lipids, smoking, HBP	ST elev. V_{1-4}	Normal
7	58/♀	10 years	↑lipids, FHx	ST elev., II, III, AVF	Abnormal ST-T waves II, III, AVF
8	40/♂	1 month	↑lipids	ST elev., II, III, AVF	Inferior MI
9	48/♂	3 weeks	Obesity	ST elev. II, III, AVF, sinus bradycardia	Abnormal T, arrhythmia
			Without coronary occlusive disease		
10	43/♂	6 years	Smoking	ST elev. II, III, AVF, arrhythmias	Normal
11	44/♀	3 weeks	FHx, ↑lipids, obesity, HBP	ST elev, I, II, III, AVF	Normal
12†	44/♀	11 years	....	ST elev., II, III, AVF, 3° A-V block, cardiac arrest	Normal

Abbreviations:
CAD = coronary artery disease
FHx = positive family history for coronary artery disease
HBP = high blood pressure
ST elev. = ST segment elevation
↑ = elevated

*All changes seen on electrocardiograms occurred during spontaneous pain and were not related to arteriography.

occurred in the precordial leads without evidence of true posterior ischemia. In the other nine, the ST elevation occurred in the inferior leads (Table 1). All twelve patients had rest pain only. It was without obvious precipitating cause and usually occurred at night.

All patients were routinely admitted to hospital and treated medically for 24 to 72 hours, at which time coronary arteriography by the Judkins technique was carried out. There were no complications from the procedure. Spontaneous spasm of one coronary artery occurred in two patients during the study. In both patients, there was spasm in an area distal to the catheter tip with associated chest pain and ST elevation similar to other documented episodes. Follow-up of these patients was obtained through the patient's private physician or from medical records.

Results (Figures 1 and 2)

On the basis of coronary arteriography, the patients can be divided into two anatomic groups. Group I consists of nine patients in whom there was severe proximal occlusive coronary artery disease of at least one major coronary artery, with or without atherosclerosis in the other arteries. Group II consists of three patients in whom there was minimal or no coronary atherosclerosis on coronary arteriography. In two of these patients (patients 10 and 11), spasm of the right coronary artery was documented during coronary arteriography. The spasm was associated with reproduction of the patient's chest pain and ST elevation on lead II of the electrocardiograph (ECG) monitor. Repeated right coronary injections documented relief of the spasm over three to five minutes with relief of the chest pain and return of the ST segments to normal. The other patient is suspected of having coronary spasm, although this was not documented during arteriography.

In the patients in Group I, the duration of symptoms ranged from three weeks to five years, with a wide variety of coronary atherosclerosis risk factors. The patients with severe occlusive coronary disease were more likely to have had a previous myocardial infarction or abnormal ST-T waves during pain-free episodes or both. The Group II patients were more likely to have had a longer history of symptoms, ranging from three weeks to eleven years, and to have a normal electrocardiogram during pain-free periods.

Patients were treated with nitroglycerin and

TABLE 1.—*Continued*

		Coronary Arteriography (percent occlusion)						
Patient	*Treadmill*	*RCA*	*Circ*	*LAD*	*LV*	*Medical Therapy*	*Surgical Therapy*	*Follow-up*
1	..	50	50	100	nl	Vasodilators, antiarrhythmics, anticoagulants	..	Improved
2	Nondiag	95	0	0	nl	Vasodilators, β-blockade	Right CAB	Improved
3	..	90	20	100	abn	..	Triple CAB	Effort Angina
4	Pos	90	0	50	..	..	Double CAB	Pain-free
5	..	0	0	90	abn	Vasodilators, β-blockade	Left CAB	Pain-free
6	..	50	0	100	abn	..	..	MI, then pain-free
7	Nondiag	95	0	0	nl	Vasodilators, β-blockade	Right CAB	Improved
8	..	>90	75	50	abn	Vasodilators, β-blockade	Double CAB	Pain-free
9	Nondiag	90	0	0	abn	Vasodilators, β-blockade	..	Improved
				Without coronary occlusive disease				
10	Neg	Spasm <30	0	0	nl	Vasodilators	..	Improved
11	Neg	Spasm <30	0	0	nl	Vasodilators, β-blockade	..	Improved
12[7]	..	<25	<25	0	nl	Vasodilators	Pacemaker	Death following prolonged chest pain

Abbreviations:
.. = not done
abn = abnormal
CAB = coronary artery bypass
Circ = circumflex artery
ECG = electrocardiogram
LAD = left anterior descending
LV = left ventricle
MI = myocardial infarction
neg = negative
nondiag = nondiagnostic
pos = positive
RCA = right coronary artery

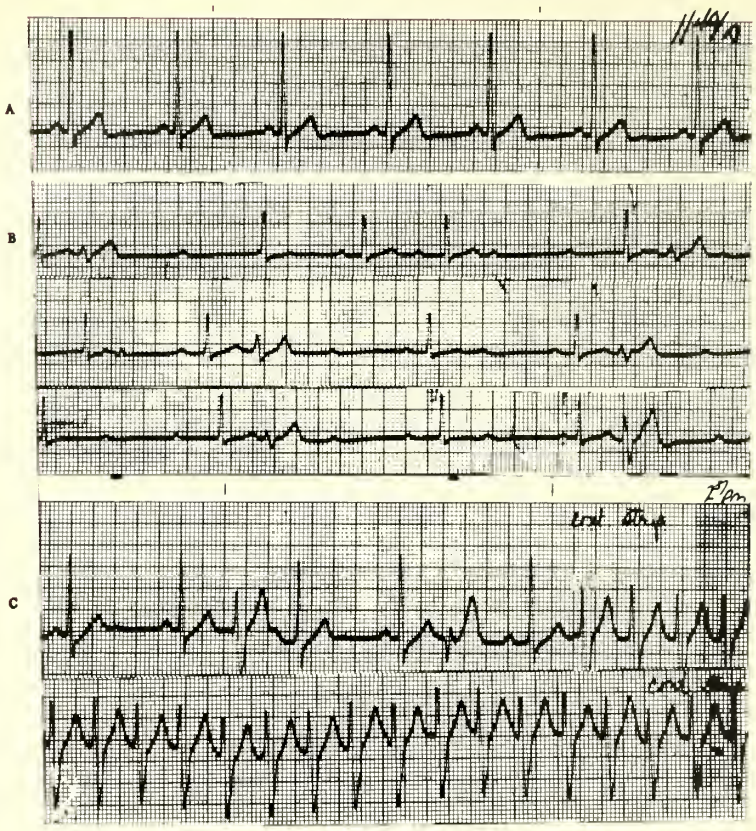

Figure 1.—Serial rhythm monitoring strips from patient 10, who had documented right coronary artery spasm during arteriography. All rhythm strips obtained during spontaneous pain episodes. **A**—normal sinus rhythm, pain-free; **B**—varying A-V block and ventricular premature contractions preceding the onset of angina and ST elevation; **C**—ventricular premature contractions and ventricular tachycardia, pain-free.

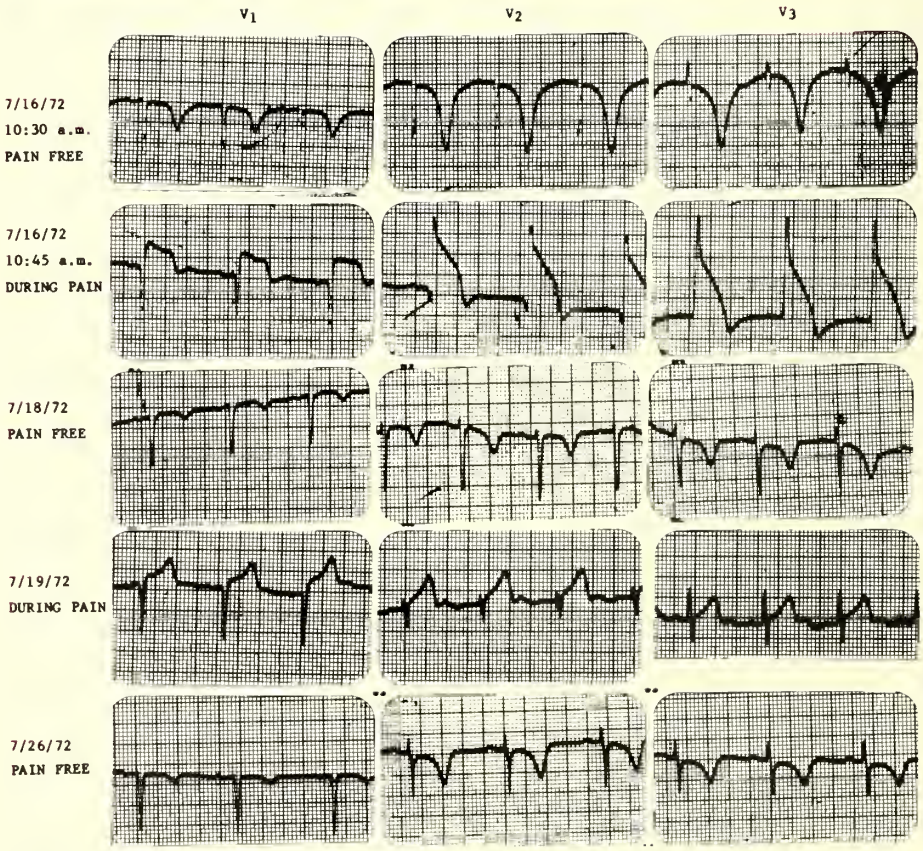

Figure 2.—Electrocardiographic leads V_1, V_2 and V_3 showing ST segment elevation and reversal of T wave inversion during pain episodes in patient 5.

long-acting vasodilators for chest pain while in the hospital. All 12 patients had moderate-to-dramatic response to vasodilators, with the greatest response noted in the patients who had only rest angina. Patients 4 and 9, who had severe occlusive coronary artery disease and positive results from exercise tests, continued to have exertionally-induced angina as well as repeated bouts of rest angina and ST elevation while in the hospital. Of the nine patients with proximal occlusive coronary disease, five have had coronary artery bypass operations without complications. Of this surgical group, three patients are free from pain, one patient has exertionally-induced angina on moderate activity and one has angina on severe activity.

The two patients with insignificant occlusive disease, but with demonstrated right coronary artery spasm, have had dramatic decrease in their chest pain following the long-term use of long-acting vasodilators and beta-blockade. In one of these patients, the addition of thorazine to the drug regimen in an effort to produce alpha-blockade resulted in little additional improvement. There was spontaneous subsidence of pain associated with enzyme elevation in one (patient 6) after a suspected acute myocardial infarction. One of the three patients without occlusive coronary disease died seven months after study, with unremitting chest pain and cardiogenic shock.[7]

Discussion

Reports in the recent medical literature have described at least 41 patients with Prinzmetal's variant angina who have been studied by coronary arteriography or postmortem examination.[2-4,6,8-13] Of the 41 patients reported, 19 had significant proximal occlusive coronary disease. One of the 19 patients had associated spasm during arteriography. There were eight of the 41 patients who had normal vessels, or less than 25 percent occlusion of the coronary arteries. Three of the eight patients had angiographically demonstrated spasm during coronary arteriography, with associated ST elevation and chest pain. This coronary arteriographic spectrum of anatomic findings is generally in accord with ours, indicating that approximately 75 percent of patients with Prinzmetal's variant angina will have severe occlusive coronary artery disease. A smaller, but important number of patients will have normal or near-normal coronary arteries. Spasm during coronary arteriography has occasionally been documented in this group. Although patients with severe proximal occlusive disease tended to have shorter duration of chest pain symptoms and were more likely to have positive findings on a treadmill exercise test, the high incidence of severe occlusive proximal disease would indicate that all patients with this syndrome should have coronary arteriography.

Our experience with treadmill exercise testing in variant angina is limited and has not been of help in differentiating the patients with coronary spasm from those with occlusive coronary artery disease. In the two patients with documented coronary spasm only, both had normal response to exercise testing at maximal heart rates of 150 and 160. Only three patients with severe proximal occlusive disease were given exercise tests; one showed a positive stress test consisting of 1 mm of ST segment depression, the second stopped the test because of fatigue with only minimal ST depression and the third had resting ST abnormalities, which precluded a definite diagnostic response during exercise. Cheng et al reported four patients with variant angina without significant coronary artery disease.[6] In one of their patients, there was ST segment elevation and chest pain during a Masters two-step exercise test. Kemp et al described a patient with ST segment elevation during exercise testing who had a severe occlusion of the left anterior descending and circumflex arteries.[9] Care must be taken in using stress testing for this patient group, however, because of the possibility of severe proximal occlusive disease and the precarious balance between myocardial oxygen demands and delivery. Stress testing should not be carried out if there is residual ST elevation on electrocardiogram or other evidence of a recent myocardial infarction, such as enzyme elevation.

In general, it is our impression that the ST elevation during exercise testing at the onset of chest pain may be indicative of severe proximal occlusive disease.

Three of our 12 patients reported had serious arrhythmias during the spontaneous episodes of chest pain (Figure 1). All three of these patients had ST elevation in the inferior leads. Two of the patients had accompanying transient atrioventricular (A-V) block. One patient had repeated bouts of ventricular tachycardia during episodes of pain, and one patient had ventricular tachycardia progressing to ventricular fibrillation. MacAlpin et al, in a study of 20 patients with variant angina, reported a 25 percent incidence of arrhythmias dur-

ing the pain period.[4] Two of their patients also had documented ventricular tachycardia or fibrillation, and two had varying degrees of atrioventricular block. In view of the high incidence of arrhythmias during chest pain, these patients require careful monitoring and may be candidates for sudden death.

The cause of the coronary artery spasm, which was initially suggested as the cause of variant angina by Prinzmetal,[1] and now documented in a number of medical reports[5,6,8] is unclear. Guazzi et al found no hemodynamic changes during chronic monitoring in patients with Prinzmetal's angina to account for a change in myocardial oxygen demands.[14] These data would suggest that changes in cardiac work are not the primary causes in the precipitation of the rest pain in this patient group. MacAlpin et al suggested that during rest and sleep the tone of the larger vessels is highest and the diameter smallest, which may predispose to coronary spasm.[11] The frequent complaint of rest or nocturnal angina in patients with Prinzmetal's variant angina is consistent with this hypothesis. These observations would suggest that patients with Prinzmetal's angina who have normal or only minimally diseased coronary arteries most likely have myocardial ischemia on the basis of changes in coronary blood flow due to coronary spasm occurring at rest.

In contrast, in patients with unprovoked or rest chest pain due to severe occlusive coronary artery disease, also called preinfarction angina, the rest angina frequently is caused by changes in myocardial work and oxygen demands. Cannom et al have documented rises in heart rate and blood pressure preceding the onset of chest pain during continuous hemodynamic monitoring in certain patients with unstable or preinfarction angina.[15] These patients with severe proximal occlusive disease may have either ST depression or elevation during their rest pain episodes. These changes noted on electrocardiograms may be the only distinguishing feature between variant angina and typical angina pectoris in this patient group.

Medical treatment is frequently rewarding in patients with Prinzmetal's angina whether they have occlusive coronary disease or normal coronary arteries. The acute episodes of chest pain with ST elevation almost invariably respond to nitroglycerin, although two of our 12 patients required narcotics for complete relief of the pain on several occasions. Of our 12 patients, seven had an excellent response to long-acting vasodilators, either prophylactically or in causing a decrease in the frequency and severity of their rest angina attacks. Guazzi et al found that chronic use of propranolol was effective in his four patients, using doses as high as 480 mg per day.[16] These authors postulated direct or secondary effects in arterial tone as a result of the propranolol administration.[14] In the two long-term patients with normal coronaries whom we have followed at Stanford University Hospital, therapy with propranolol and vasodilators has been satisfactory in relieving approximately 75 percent of disability caused by pain. In view of this excellent response to medical therapy, we do not believe that coronary bypass operation is indicated in patients with normal or minimal coronary artery disease.

MacAlpin et al suggested that denervation by adventitial stripping, coupled with coronary artery bypass operation in instances of severe occlusive disease, may alleviate the problem of recurrent spasm at or beyond the site of bypass.[4] Of those in our patient group in whom coronary artery bypass surgical procedures were carried out, one patient has had recurrent angina following triple bypass operation, but not of Prinzmetal's type and not associated with ST elevation; three patients have been pain-free for three months, six months, and one and a half years, following operation, and the remaining patient has had pronounced improvement.

Conclusions

- Prinzmetal's variant angina is a spectrum of clinical presentations with pronounced variation in coronary arteriographic anatomic findings, rather than a specific anatomic disease entity. It is characterized by symptoms of spontaneous chest pain with or without radiation to the neck, shoulders, jaws or arms, which occurs at rest and is associated with ST segment elevation during chest pain, but without progression to frank myocardial infarction upon resolution of the pain.
- Patients with normal findings on resting electrocardiograms, a negative response to a treadmill exercise test and a long history of rest angina are more likely to have normal or minimally diseased coronary arteries. Despite this, the high incidence of severe proximal occlusive coronary disease indicates that all patients should have coronary arteriographic study.
- Short- and long-term medical treatment includes short-acting vasodilators, to which there is usually an excellent response. Patients fre-

quently respond to long-acting vasodilators such as isosorbide dinitrate, given both prophylactically and to decrease the frequency and severity of attacks. Propranolol has occasionally been helpful in these patients and can be tried in those patients with minimal coronary artery disease.

- Coronary artery bypass operation should be considered only for the patient with high-grade proximal occlusive coronary lesions.

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Erythroblastemia

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The significance of erythroblastemia must be considered in the context of the clinical setting in which it is found. Interpretation should take into account the number and spectrum of maturity of the nucleated red cells; the presence or absence of reticulocytosis and other red cell abnormalities (for example, poikilocytosis); the presence or absence of anemia; the presence or absence of circulating immature granulocytes or bizarre platelets and the presence or absence of the spleen. Circulating nucleated red cells indicate intravascular hemopoiesis or disruption of marrow structure or the inability of the bone marrow's screen mechanism to prevent their passage into circulation. In the latter situations, it usually indicates an unfavorable prognosis.

THE TERM ERYTHROBLASTEMIA describes the presence of nucleated red cells in circulating blood.

Erythroblasts are not found in the blood of healthy persons in whom the increased demand for red cells is met by an orderly delivery of reticulocytes into circulation. Thus, erythroblastemia indicates an underlying disorder. An exception is the newborn infant in whom a few nucleated red cells may normally be present in blood during the first week.[1-5] Prematurity, anemia or obstetrical complications resulting in antenatal hypoxia, may intensify this otherwise normal finding.[5,6] Presumably, erythroblastemia in the normal neonate results from a lack of maturity of those mechanisms that serve to keep these cells out of circulation.

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Paul Ehrlich was the first to describe the presence of nucleated red cells in the blood. In 1880, shortly after his introduction of staining methods in hematology, he wrote a paper, "Findings in Anemia—De- and Regeneration of Blood Cells," in which he differentiated between the "normoblasts" present in the anemia of blood loss and the "megaloblasts" present in pernicious anemia.[7] The latter, said Ehrlich, were the precursors of giant red cells present in the condition, and he coined the term "megaloblast." Before 1929, when the examination of marrow aspirates was introduced into the practice of hematology, the diagnosis of pernicious anemia was frequently established by demonstrating megaloblasts in blood.

Red Cell Delivery

Erythroblastemia is seen in association with a variety of hematologic and nonhematologic disorders and indicates a breakdown of the normal mechanisms of the red cell proliferation and delivery. In man, normal production of blood cells

occurs in the extravascular spaces of the bone marrow (hemopoietic compartment),[8] mature cells being delivered into circulation in an orderly fashion according to body demand. The factors controlling the movement of mature cells from the hemopoietic compartment into the circulation are poorly understood. Nucleated red cells may actively participate in this movement as they are capable of ameboid motion.[9] Minor variations in intramedullary pressure, resulting from cellular proliferation, may also be a factor.[10,11] It is helpful to consider that the hemopoietic tissue is located within the nonexpansile bony cavity of fixed volume. As each new cell grows, one must depart so as to maintain the fixed volume. Thus, cell traffic out of the marrow cavity varies proportionately with the intensity of cell proliferation in the hemopoietic compartment.

The endothelium of marrow sinuses contains actual, or potential, openings through which cells from the hemopoietic compartment gain access to circulating blood.[8,12-14] Nucleated red cells attempting to enter the circulation lose their nuclei as they negotiate the rigid pores of the sinus endothelium that permit passage of the plastic cytoplasm but hold back the rigid nucleus.[15] There is evidence to indicate that the sinus endothelium, acting in concert with the surrounding (perisinal) macrophages, exerts a control on the flux of cells into the circulation. The cytoplasmic projections of these macrophages cover the pores, totally or partially. The extent of this coverage may change according to the intensity of cell traffic, providing a sieve of variable area to the passing cells.[8,16,17] It is, in part, through this "sinus sieve" that the body's demand for blood cells is translated into the rate of cell delivery to the circulation by a mechanism in which erythropoietin may play a part.

This control mechanism is not absolute, however, and occasional nucleated red cells may escape into the circulation. Because of their rigidity, such cells are trapped within the microcirculation of spleen and either enucleated or destroyed.[18,19]

Mechanisms of Erythroblastemia

From a pathophysiologic standpoint, erythroblastemia may occur under four circumstances:

1. The rate of hemopoietic cell production may override the capacity of the "sinus sieve" to keep the blood free of nucleated red cells. The hyperproliferation of erythropoietic tissue within the nonexpansile confines of the bone cavity may force more nucleated red cells into circulation than the sinus sieve or the splenic filter can screen out. This erythroblastemia is usually limited to a few fairly mature nucleated red cells, the number of which reflects the severity of the underlying disease. In such disorders an appropriate reticulocytosis is usually present.

2. On the other hand, when the increase in demand for erythrocyte is acute, the sinus seive is overwhelmed and some nucleated red cells may escape into circulation before the development of significant erythroid hyperplasia. This may be the mechanism of erythroblastemia in severe blood loss with attendant hypotension and hypovolemia. This mechanism is probably mediated by an increase in production of erythropoietin as a result of hypoxia. Increase in erythropoietin output may also be responsible for erythroblastemia accompanying hypoxia of severe cardiac failure, pulmonary embolism or severe cor pulmonale. In these situations, the findings of erythroblastemia is often indicative of unfavorable prognosis. Slight to moderate reticulocytosis (up to 8 percent) may be present. Erythroblastemia is restricted to fairly mature nucleated red cells, but occasional immature granulocytes may also be seen. Morphologic abnormalities of red cells are usually absent.

3. A third cause of erythroblastemia is mechanical disruption of the normal marrow structure by infiltrative diseases, notably metastatic carcinoma. This form of erythroblastemia is usually accompanied by the presence of circulating immature granulocytes and severe anemia (leukoerythroblastic anemia) and carries a poor prognosis. The circulating nucleated red cells may be in all stages of developmental maturation.

It is of interest that not every metastatic carcinoma with marrow involvement is associated with erythroblastemia. Some tumors (prostate, breast, lung) show a greater tendency than others to produce this phenomenon. The reason for this is not clear. Ehrlich and Lazarus, the first to appreciate the significance of erythroblastemia in this situation, were also puzzled by this discrepancy. They suggested that in the disruption of marrow structure "the mechanical factor is of less importance than the highly concentrated metabolic chemical products of the tumor which act on the motile cells in a negative chemotactic way."[20]

4. Another cause of erythroblastemia is hemopoiesis within the intravascular space—a phenomenon that bypasses the sinus sieve.[21] This is

seen in the myeloproliferative disorders, notably myeloid metaplasia, polycythemia vera, Di Guglielmo's syndrome and chronic granulocytic leukemia. In these disorders, particularly myeloid metaplasia, with or without myelofibrosis, poikilocytosis is often profound as deformed cells proliferate directly within the blood stream in teardrop and other abnormal forms. The appearance of bizarre platelets and immature granulocytes in the circulation (leukoerythroblastemia) is also explicable on the basis of intravascular hemopoiesis. As may be expected, nucleated red cells in all stages of development (basophilic, polychromatophilic, orthochromatic) are seen in the blood. Mild reticulocytosis (2 to 5 percent) is usually present as well.

It is of interest that when patients with myeloid metaplasia and myelofibrosis are treated with androgens for anemia, the number of nucleated red cells in the blood may increase considerably.[22,23] This increase has its counterpart in reticulocytosis that occurs in aplastic anemias in response to androgens. In myeloid metaplasia, however, erythropoietic stimulation occurs within the vascular compartment resulting in an increase in circulating nucleated red cells.

Circulating hemopoietic cells, irrespective of the way in which they enter circulation, are trapped in the spleen, and if such cells are able to undergo mitosis, they may form small hemopoietic foci.[19] Some investigators have implicated such foci of hemopoiesis as the pathogenetic *cause* of erythroblastemia.[24-26] These foci are, however, extravascular, being located in the cordal compartment of splenic red pulp. They are the *result* of erythroblastemia. Extramedullary hemopoiesis may be intravascular or extravascular. To implicate extramedullary hemopoiesis as a cause of erythroblastemia, intravascular hemopoiesis must be demonstrable.[27]

Splenectomy, by removing the splenic filter, intensifies the degree of erythroblastemia that may have been present before removal of the spleen, particularly in patients with myeloid metaplasia and myelofibrosis, and in some patients with chronic hemolytic anemia (for example, thalassemia).

It may not always be possible to define a single mechanism for erythroblastemia. Indeed, a combination of mechanisms may exist in some diseases. In the leukemias, for instance, intense cellular proliferation in the hemopoietic compartment may override the ability of the screening system, and patchy destruction of marrow structure may also play a part.

Clinical Significance

The finding of erythroblastemia may be of diagnostic and prognostic aid to the physician in the following clinical circumstances:

Neoplastic marrow infiltration

The finding of nucleated red cells on a routine blood film may herald a neoplastic disorder.[20,24,28-32] Both hematologic and nonhematologic neoplasms should be considered. Among the hematologic neoplasms, myeloproliferative disorders are most commonly associated with erythroblastemia, although myelomatosis, Hodgkin's disease and other lymphomas may be associated with this finding. A complete physical examination and hematological workup, including bone marrow examination, often yield clues to the diagnosis.

Among the nonhematological neoplasms, bone-seeking carcinomas, including those of prostate, breast, lung, thyroid and gastrointestinal tract, should be considered. In all instances a needle biopsy of marrow may yield more diagnostic information than a marrow aspiration in establishing the carcinomatous origin of erythroblastemia. Further workup is, however, necessary to establish the origin and extent of neoplasm. When erythroblastemia is found in a patient with known carcinoma, it implies extension of the disease to the bone marrow.

Non-neoplastic infiltrative diseases

Erythroblastemia has been reported in association with non-neoplastic infiltrative disorders of the bone marrow such as marble bone disease (Albers-Schonberg), osteitis fibrosa cystica (von Recklinghausen's disease), Gaucher's disease, and other lipoidoses.[20,28,32] These are, however, rare disorders and erythroblastemia is not a common manifestation. When it is found, it is usually mild to moderate and the diagnosis of the underlying disease is easily established.

Cardiac failure

Erythroblastemia in cardiac failure indicates a poor prognosis.[25,29,33-35] Cyanosis and hypoxemia are invariably present. Urinary erythropoietin levels, however, may or may not be elevated.[35] The cardiac failure is usually "right-sided," often associated with chronic obstructive pulmonary disease

or pulmonary infarction. Erythroblastemia has also been reported in association with "cerebral vascular accidents,"[28] but the documentation of ancillary disorders in these patients has been inadequate. Such patients may have associated cardiac failure or pulmonary thromboembolism and erythroblastemia could have resulted from these complications.

Hemolytic diseases

Among the hemolytic anemias,[20,24,29,32] erythroblastosis fetalis and thalassemia major are most commonly associated with erythroblastemia. The latter disease is sometimes referred to as erythroblastic anemia. In other hemolytic anemias, erythroblastemia is usually not severe unless the spleen is absent. Compensated hemolytic diseases (without anemia) are not usually associated with erythroblastemia. Erythroblastemia may also be seen in conditions associated with ineffective erythropoiesis such as pernicious anemia or sideroblastic anemia.

Iron deficiency and blood loss

Nucleated red cells may be seen in blood from patients presenting with iron deficiency anemia.[36] This occurs most commonly in those cases with either very low hemoglobin concentrations or high reticulocyte counts. Because in the absence of active bleeding, reticulocyte count is not elevated in iron deficiency anemia, it is likely that erythroblastemia in these cases is a result of active bleeding and the bleeding site should be sought.

Kidney graft rejection

The appearance of nucleated red cells in the blood following renal allograft, may herald an imminent rejection of the grafted kidney.[37-39] In this setting, erythroblastemia may or may not be associated with polycythemia. The bone marrow shows erythroid hyperplasia, serum and urinary erythropoetin levels are elevated, and reticulocytosis is present and correlates with erythropoietin levels.[38-41] It is generally believed that the increased erythropoietin output resulting from renal hypoxia associated with graft rejection is responsible for both the erythroblastemia and the polycythemia. When splenectomy is done as an additional means of impairing the immune response, erythroblastemia may be striking in this situation with figures as high as 500 nucleated red cells per 100 leukocytes reported.[37,38]

Infections

Erythroblastemia has been reported in a wide variety of infections.[24,29,32] It is usually considered to be part of leukemoid reaction in response to the infection. It must be emphasized that well-documented leukemoid reactions have only been reported in tuberculosis where successful treatment has been known to normalize blood conditions,[42,43] and where some experimental basis for its occurrence has been provided.[44] Tuberculosis is usually of the miliary type, and in most cases the leukoerythroblastemia is associated with leukocytosis, although in a few cases leukopenia may be present.[45] Even in tuberculosis, leukoerythroblastemia is a very uncommon finding. In other situations where infection has been reported in association with a leukemoid reaction, the presence of an underlying myeloproliferative disorder has not been satisfactorily excluded. Patients with myeloproliferative disorders are usually susceptible to various infections and it is probable that such reports represent cases of undiagnosed myeloproliferative disorders with superimposed infection.

Attempts have been made to identify the nature of underlying disorders according to the severity of erythroblastemia.[24] In hemolytic anemia and following acute blood loss, only a few circulating normoblasts are seen. Erythroblastemia is moderate in severe pernicious anemia and cardiac failure, whereas in myeloid metaplasia, erythroleukemia and metastatic carcinoma, it may be intense. This correlation generally holds in clinical interpretation but is far from finite. Values as high as 500 normoblasts per 100 white cells have been reported in sickle cell anemia.[24]

Erythroblastemia is conventionally quantified by counting the number of nucleated red cells per 100 leukocytes seen in blood films. Because nucleated red cells are not distinguished from leukocytes in either chamber or automatic white cell counts, the reported absolute value for the leukocyte count is the sum of the white cells and nucleated red cells. To obtain the true, or corrected, leukocyte count, the number of nucleated red cells per 100 leukocytes should be determined by differential count and the following formula used:

$$\text{corrected leukocyte count} = \frac{\text{reported leukocyte count} \times 100}{\text{nucleated red cells} + 100}$$

Occasionally there are too few nucleated red cells present in the circulation for detection on routine blood films, but their presence can be readily identified in a buffy coat preparation.

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Myelodysplasia

Problems of Long-Term Survival and Social Function

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Problems of ninety-eight patients with myelodysplasia, ages 13 to 72, were reviewed. They were grouped as follows: Those having thoracic and high lumbar level ($L_2\uparrow$) lesions and confined to wheel chairs, those with intermediate paralysis ($L_{3\text{-}5}$ nerve roots) as walking with aids and those with less paralysis ($S_1\downarrow$) as fully ambulatory. Fifty-two percent of the $L_2\uparrow$ and only 15 percent of of the less severely paralyzed patients were retarded below an IQ level 70 ($P<0.01$). Thirty-six patients (62 percent) were fully and 26 partially, but appropriately, self-sufficient. Thirty-six patients were found in some form of dependent care. Two of the 71 more paralyzed patients ($L_{3\text{-}5}$ and $L_2\uparrow$) and five of the 28 $S_1\downarrow$ patients were "naturally continent" but reported stress incontinence of urine. Thirteen of 23 female and five of 28 male patients between ages 16 and 72 years reported sexual activity and accounted for 17 normal offspring. All 23 retarded patients were in some form of custodial care. Dependency among the normal intellect patients could be attributed to neglect of physically deforming complications and emotional disorders, primarily low self-esteem centering around social and sexual identity problems associated with excrement soiling.

THE LITERATURE CONTAINS little information about teenage or adult patients who were born with myelodysplasia. In 1952 Fisher et al reported[1] survival of 471 myelodysplasia patients, 17 percent of whom were between the ages of 20 and 53 years. They did not mention functional status. Four groups of investigators[2-5] have described the functional status of 83 adults and teenagers wtih congenital paraplegia. Most were under-achieving in school, in employment and in performance of self-help skills when compared with patients who had similar degrees of acquired paralysis. Genetic studies report four myelodysplastic children have been born among 114 children of 226 living myelodysplastic adults.[6,7] These latter two studies imply a relatively effective social adaptation but contain no descriptive details.

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TABLE 1.—*Intellectual Performance*

Functional Spinal Neuromuscular Level	DEGREE OF MENTAL RETARDATION: Profound to Moderate	Mild	Borderline	Normal	Bright Normal	Superior and Very Superior
	RANGE IQ SCORES					
	<51* <54†	52-68* 55-69†	69-83* 70-84†	84-110* 85-109†	111-120* 110-119†	121* and > 120† and >
$L_2\uparrow$ (N=27)	9(33%)	5(19%)	4(15%)	8(30%)	0	1(3%)
$L_{3\text{-}5}$ (N=43)	4(10%)	1(2%)	8(20%)	22(50%)	5(12%)	3(6%)
$S_1\downarrow$ (N=28)	2(7%)	2(7%)	6(21%)	13(47%)	3(11%)	2(7%)

( ) = % of patients by level of lesion.
*SB = Stanford Binet.
†WISC = Weschler Intelligence Scale for Children.

TABLE 2.—*Summary of Social and Educational/Occupational Function for Myelodysplasia Patients With IQ Greater Than 70*

Functional Status	Level of Lesion*	Age in Years: 13-18†	19-26‡	Older than 27 Age in ( )
Fully employed or housewife with complete self-help skills	$L_2\uparrow$	0	3	1 (51)
	$L_{3\text{-}5}$	0	2	2 (30 & 73)
	$S_1\downarrow$	0	3	2 (34 & 34)
Normal grade in school or in higher education & complete self-help skills	$L_2\uparrow$	0	0	0
	$L_{3\text{-}5}$	10	3	0
	$S_1\downarrow$	8	2	0
Living at home or in custodial care with partial self-help skills and in special education or job training	$L_2\uparrow$	6	1	0
	$L_{3\text{-}5}$	11	2	0
	$S_1\downarrow$	4	2	0
Custodial care or living at home with no program	$L_2\uparrow$	0	2	0
	$L_{3\text{-}5}$	1	5	2 (57 & 34)
	$S_1\downarrow$	0	2	0

*See text for definition.
†Age range eligible for grade or high school.
‡Age range eligible for college and higher education.

Most observers reporting upon older patients describe a group of patients referred to their institutions for rehabilitation—that is, selected. We have studied nearly all living myelodysplastic patients in our area (we were not able to trace three patients), regardless of the degree of handicap. The purpose of this report is to describe the intellectual capabilities, neuromuscular function, educational and economic status, and social adaptation of 98 myelodysplastic patients between the ages of 13 and 73 years.

Method

Patients born with myelodysplasia (for example, spina bifida aperta, myelomeningocele, meningomyelocele) were brought into this study through record reviews and health department birth records. Most have been followed for up to 17 years in a multiple disciplinary clinic. All clinical data have been recorded on standardized record forms and analyzed for survival using the conversational computer statistical service.[8] We have derived information concerning the presence and treatment of hydrocephalus, intellectual performance and various types of self-help skills from these computer records (28 items). Current social and economic or educational status were added. Intellectual assessments were obtained by a battery of gauges including the Weschler Intelligence Scales for Children (and Adults), Wide Range Achievement and Stanford-Binet tests.

Grading of muscle strength was recorded according to the Sharrard classification.[9] Grouping of our patients was made by functional motor activity as follows:

- Lesions at or above the second lumbar vertebra ($L_2\uparrow$)—All thoracic and lumbar root levels 1 and 2—intercostal, abdominal and hip flexion and adduction muscles function—essentially all wheelchair patients.
- Lesions between the third and fifth lumbar vertebrae ($L_{3\text{-}5}$)—Additional muscle strength in quadriceps and hamstrings giving stronger hip flexion and adduction with knee flexion (weak) and extension; some patients have anterior tibialis with weak foot dorsiflexion and weak hip abductors—most walk effectively with aids, surgical operation and extensive bracing.
- Lesions at or below the first sacral vertebra ($S_1\downarrow$)—Additional muscle strength about the ankle with variable degrees of hip abduction and extension—essentially all walk with minimal aids.

Confirmation of sexual activity for women was based on history, with the majority confirmed by pregnancy. Confirmation of male activity was accepted only with corroborating evidence.

Educational or occupational and social func-

TABLE 3.—*Reasons For Failure to Achieve Expected Goals—Custodial Care Without Program (12 Patients)*

Level of Lesion	*No. Patients*	*Age In Years*	*Sex*	*Untreated Complications*	*IQ*	*Major Cause for Failure*	*Other Comments*
$L_2\uparrow$	2	20*	♀	Yes	105	Scoliosis, decubiti, urine soilage	Family rejection
		20	♀	Yes	75	Family rejection and personal psychological problems	Obesity, poor motivation
$L_{3\text{-}5}$	8	18†	♂	No	90	Family psychopathology, disturbed child with poor motivation	Urine soilage, school dropout
		19†	♀	Yes	80	Early educational deprivation, family rejection, obese	Married to mental retardate, wheelchair, IQ=61 at age 14 yrs; after special educ., employed as telephone operator briefly
		24†	♂	Yes	112	Psychosexual disturbance, condom drainage with poor hygiene	Penile slough, lack motivation
		24	♀	No	70	Psychosexual pathology, sexually permissive	.....
		24†	♀	No	95	Psychosexual pathology, family psychopathology	Unwed mother
		24	♀	No	70	Psychosexual pathology	Sexually active, school dropout
		34†	♂	Yes	122	Psychosexual pathology, lack motivation	Dropped out of work despite graduate degree; sexual fantasy life
		57†	♂	No	127	Coronary artery disease, celibate, over-concerned about hygiene	Lost position, now unable to find employment despite graduate degree
$S_1\downarrow$	2	21†	♂	Yes	70	Family rejection	Married, both partners with venereal disease, patient's child put in custody
		22	♂	Yes	115	Dying of renal failure, lacks motivation, psychosexual pathology	Urine soilage

*Only patient totally bedridden. All others are capable of feeding, dressing, personal hygiene and self mobility.
†Living at home on welfare subsidy.

tion were defined as independent or custodial living, complete or appropriate partial (for example, teenagers too young to drive), or no self-help skills and normal grade placement in school or employment, or special education, sheltered workshops or special job training.

Observations

Complete information, examinations, and tests were obtained for 98 patients. Three additional patients could not be contacted for this study.

Intelligence

Intellectual performance has been recorded in Table 1. Fifty-two percent of patients with $L_2\uparrow$ level lesions were classified in the profound to moderate or mild retardation group as compared with only 15 percent of the lower level lesion patients ($X^2=12.8$, df=1, $P<0.01$) and 6 percent of the general population.

Occupational or Educational and Social Status

A summary of the occupational or educational and social status of the patients with borderline, normal, or better than normal intellect has been recorded in Table 2. Among 36 patients who are completely self-sufficient and in either normal academic level or fully employed, there are ten with severe organic or social adjustment complications (above solid line in Table 2). One father

TABLE 4.—*Reasons for Failure to Meet Expected Goals—Living at Home or in Custodial Care in Special Education or Job Training (11 Patients)*

Level of Lesion	*No. Patients*	*Age*	*Sex*	*Capable of Self-Help Skills*	*Untreated Complications*	*IQ*	*Major Cause for Under-performance*	*Other Comments*
$L_2\uparrow$	4	13	♀	Partly	Yes	97	Family psychopathology, renal failure	Scoliosis, obesity, lack of motivation
		14	♀	Partly	Yes	90	Family psychopathology	Dislocated hips, recurrent fractures of legs, poor urine hygiene
		16	♀	Partly	No	75	Lack of motivation; three CNS infections	Scoliosis
		19	♀	Partly	Yes	75	Huge head, renal hypertension	Recurrent decubiti, lack of motivation, denied early Rx
$L_{3\text{-}5}$	5	13	♀	Yes	No	72	Seizures, poor family situation	Foster care, low intellect, divorced parents
		16	♀	Partly	No	70	Family rejection	Urine soilage, placed in an institution
		17	♀	No	No	77	Spastic quadriplegia	Excellent care—medical, school and home; severely handicapped following shunt obstruction and CNS infection
		19	♂	Yes	Yes	70	Neurologic sequelae of untreated hydrocephalus	Severe decubiti and osteomyelitis, secondary to urine soilage; family rejection
		21	♂	Yes	No	77	Family rejection	Urine soilage
$S_1\downarrow$	2	13	♂	Partly	No	70		
		14	♂	Partly	No	70		Urine soilage

with three children is dying of renal failure.* Severe decubitus ulcers and osteomyelitis developed in an unmarried young man causing reduction in his locomotor status from ambulation with Lofstrand crutches to a wheelchair. Both of those patients had sacral level lesions. Three unmarried young men have serious emotional problems, in part relating to urine incontinence and difficulty with sexual adjustment. Two young women have been disappointed by broken engagements and one has been left an unwed mother. Two other young women, though interested in men, are ineffective in relating to them. The other 26 appear to be well adjusted and are either making good progress toward or have achieved social stability and self-sufficiency.

Twelve patients (below the dashed line in Table 2) have failed to perform in an expected social, occupational or educational manner. Reasons for failure, usually multiple, are recorded in Table 3.

*Patient died eight months after study was completed.

Twenty-six patients (ages 13 through 26) were intermediate between the above two groups because of (1) young age, or (2) they are still in an educational or training status and (3) because of a low intelligence quotient. Eleven of these 26 are not expected to succeed, for reasons stated in Table 4. Considering their handicap, the others were progressing well in school or special education and medical rehabilitation programs. If their progress continues, they can be expected to become fully self-sufficient.

Urine Control

Only one female patient among the 27 patients with $L_2\uparrow$ and one among the 43 with $L_{3\text{-}5}$ level lesions have developed socially acceptable natural continence of urine. Two female and three male patients among 28 with $S_1\downarrow$ lesions (17 percent) have some degree of urinary continence. However, frequent stress incontinence causes social embarrassment for most of these seven pa-

TABLE 5.—*Method of Urine Collection, Teenage and Adults, 1973*

	Socially Satisfactory	*Socially Unsatisfactory*	*Biologic Complications*
Early Ileal Diversion	28(93)†	0	2
Late Ileal Diversion	4(28)	0	10
MR and Diaper ...	14(82)	0	3
Natural Drain	6(86)	0	1
Napkin/Diaper ..	2(25)	5	1
Sheath	5(63)	2	1*
Clamp	1(50)	1	0
Catheter	3(60)	1	1*
Ureterostomy	0	0	1
Suprapubic	0	0	2*

*One each now with satisfactory loop.
†Figures in ( ) are percentages.

TABLE 6.—*Sexual Activity in 51 Myelodysplastic Patients, Age 16-72*

	Male	*Female*	*Totals*
No Sexual Activity: ...	23	10	33
Too handicapped ...	14	4	18
Virginal	9	6	15
Sexual Activity:	5	13	18
Premarital	1	8	9
Marital	3	3	6
Both	1	2	3
TOTALS	28	23	51

tients. Methods of urine collection for the other 91 known patients have been recorded in Table 5. Satisfactory urine control was best in patients who had ileal diversion early. Recurrent urinary tract infections, stone formation and the persistence or progression of hydronephrosis occurred following diversion only where the diversion was not performed until after the onset of hydronephrosis and ureterectasis.

Sexual Activity

Sexual activity of 51 patients between the ages of 16 (youngest patient involved) and 72 years is recorded in Table 6. Eighteen of these 51 patients were judged to be participating in sexual activity. Several with colorful but unconfirmed stories were not included. Female patients had premarital sexual relations more frequently than males ($P<.01$). Both male and female patients described varying degrees of gratification and pleasure from sexual intercourse. Only one woman described occasional painful or unpleasant sensations with coitus. Although only one of the five involved men experienced erection, manual penile manipulation at the introitus provided adequate satisfaction. One sired three children. All of the 17 offspring from these myelodysplastic parents have been normal. Each of the two women with ileal diversion who have borne a child requested tubal ligation because of urinary tract infections, urinary obstruction, and ileal loop stoma difficulties in the third trimester.

Social Attainment of Retarded Patients

Social function and educational status for 23 retarded myelodysplastic patients ages 13-22 years were limited. None of these 23 patients shows evidence of being able to achieve an independent social life. Eighteen are profoundly to

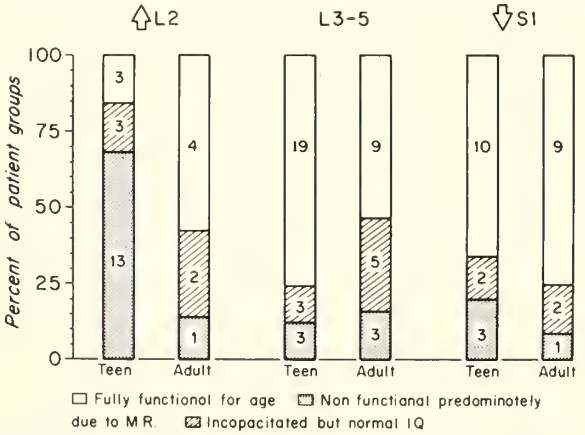

Chart 1.—Attainment of teenage patients with myelodysplasia compared with that of adult patients.

severely retarded (IQ of 10 to 50). Ten of these had $L_2\uparrow$ level lesions. All 18 patients have a combination of physical deformity and low intellect that render them bed-care patients. The other five patients, less retarded, were in custodial care but had partial self-care abilities and were engaged either in special education or job training (IQ of 51 to 66). Only one of the latter group is not in the $L_2\uparrow$ level lesion group. Total custodial care costs $6,500 a year, whereas partial to complete self-care reduces the cost to an average of only $1,500 a year.

Comparison of Teenage and Adult Attainment

Chart 1 compares the attainment for teenage patients (13 to 18 years of age) with that of adults (19 years and older). Approximately the same proportion of teenagers as adults with $S_1\downarrow$ lesions are fully functional for age, are incapacitated physically but with normal IQ, or are in custodial care. Eighty-four percent of the high level lesion ($L_2\uparrow$) teenagers are in custodial care due to physical disabilities, mental retardation, or both. This proportion of non-functional teenagers is twice that of similarly paralyzed older patients

($.02 < P < .05$). That more teenagers than adults in the L_{3-5} paralysis group are fully functional is of questionable significance ($.05 < P < 0.1$). In the six-year teenage lifespan there are many more survivors (59) than the 41 adults representing the older seven decades of life ($X^2 = 44$, $df = 1$, $P < 0.001$). Four (10 percent) adults (1 with $L_2\uparrow$ and 3 with L_{3-5} level paralysis), and 15 (26 percent) teenagers (9 with $L_2\uparrow$, 5 with L_{3-5} and 1 with sacral level lesions), have shunt treated hydrocephalus ($X^2 = 3.2$, $.05 < P < 0.1$). Eight of the 19 with shunts are retarded (42 percent) compared with 15 of 79 patients without shunts (19 percent) ($X^2 = 3.4$, $df = 1$, $.05 < P < 0.1$).

Discussion

Few infants born with myelodysplasia and active or progressive hydrocephalus are currently surviving as adults.[15] Survival to adulthood can now be expected for 60 to 70 percent of infants referred to a regional center.[14,15,29,30] There are, however, too few long-term studies for an accurate prediction. Survival of treated hydrocephalic children has risen from 60 percent in 1963 to 90 percent in 1974 in our own center.[31,32] Earlier referral, more appropriate selection, more effective spinal fluid shunt systems, improved understanding of shunt complications and treatments, as well as availability of broader spectrum antibiotics may account for this better survival. Hence, of the one myelodysplastic baby in fifteen hundred births in the United States, probably 50 percent will survive to adulthood through use of currently accepted methods of treatment.

Even without early intervention, a number of myelodysplastic patients have survived to adulthood with varying degrees of lower extremity paralysis. Many have no evidence of hydrocephalus although some have enlarged heads or a (poorly documented) history of rapid head growth in infancy. Our 41 adults and most of our older teenagers have managed to survive with arrest of hydrocephalus in a way comparable to that of other patients mentioned in the literature.[1-5] High level motor lesions observed in these older patients may have been originally low level motor lesions that became locally infected, traumatized, or scarred. The more common occurrence of mental retardation among those with high level lesions is probably associated with cephalad neural tube dysplasia that is coincident with failure of the caudal neuropore to close.[10,11] Lower level lesions may occur more frequently from coalescence of distal neural elements[12] and, therefore, may be less frequently associated with cephalad dysplasia and mental retardation.

Irrespective of types of reconstructive and educational care provided in later life, primary brain malformation may explain the increased proportion of mental retardates in our young teenage population and in the studies of other young patients.[4,13-16] The data in this study only suggest that the increase in survival of myelodysplastic, teenage patients is related to the survival of a greater proportion of mentally retarded, shunt-dependent patients.

Untreated, neuromuscular imbalance across joints can cause contractures and scoliosis that impede or prevent self-mobility. Asymmetric weight-bearing secondary to contractures as well as neurogenic anesthesia can cause severe perineal decubitus ulcers. The incidence of ulcers increases considerably with excretory soiling.[17,18] Untreated decubitus ulcers, by extending infection to soft tissue, bone and joint have reduced some of our patients from walkers to wheelchair or bed existence.

In addition, myelodysplastic patients suffer from emotional consequences of incontinence.[3,5,17,18] Emotional disturbances stem from low self-image, excreta soilage, and odor ("outhouse syndrome"), poor motivation, lack of opportuntiy for heterosexual intimacy and poor sexual identity. Congenitally paraplegic patients can enjoy sexual activity and reproduce just as do those whose paralysis is caused by trauma.[5-7] Some exaggerate their sexual prowess even more than do their "normal" peers of the current culture. Regardless of the degree of fact or fancy, management of urine collection should take into consideration the need for sexual adaptation. Urine collection devices such as the penile clamp, sheath collector, Foley catheter and suprapubic cystotomy tube have led to severe physical complications secondary to adolescent rebellious misuse of them, as well as to deep-seated emotional scars.

Several female patients were inappropriately advised about their fertility, and unexpected pregnancy followed. Appropriate reproductive counseling should include five separate concepts:

- Male and female paraplegic patients describe gratification as a result of sexual play.[5]
- Female paraplegic patients can conceive.[6,7] In the absence of complicating infections that could produce secondary sterility and despite erectile impotence, adult male paraplegic patients are fertile, if they ejaculate.[6,7] It is possible for a male

patient born with a flail penis to have insertion of an artificial, prosthetic corpora erecta[19] and an internal urinary bladder sphincter[28] to prevent retrograde ejaculation.

- Approximately 3 percent of children born of a myelodysplastic parent are born with a neural tube defect.[6,7]
- Amniocentesis can identify affected fetuses.[20]
- A paralyzed patient with an ileal diversion, in our experience, has a difficult and hazardous third trimester of pregnancy.

Under-achievement is more common in the celibate male suffering from low self-esteem. This lower self-image is derived in good measure from physical impotence compounded by antisexual urine collection devices. Preoccupation with sex and an apparent compulsion to bear children to prove femininity can interfere with social adjustment of female patients.

The effect of mental retardation on the performance of older patients, and insidious urinary tract deterioration leading to irreparable hydronephrosis suggest the need for two types of preventive care early in the life of myelodysplastic patients. To provide for the highest possible quality and length of life, the patient must be protected against the sequelae of hydrocephalus and hydronephrosis. Modern advances in cerebrospinal fluid management[21-23] and control of shunt-related infections[24] provide the means for protecting the central nervous system against pressure effects and damage from infection. Frequent urinary tract evaluation and use of ileal diversion before the onset of hydronephrosis and hydroureter have preserved renal health of patients in this as well as in other series.[25-27] It may be hoped that urinary bladder outlet relaxing procedures combined with the insertion of a silastic, internal, extravesical artificial urine sphincter will provide even more aesthetic care for the neurogenic bladder in the future.[28]

Treatment of myelodysplastic patients should be directed at enhancing locomotion, aesthetic urine and stool control and self-care both for those with normal intellect and the mentally retarded. An infant with normal or potentially normal intellect should have life-sustaining treatment of potentially fatal central nervous system and urinary tract problems. A distinction should be made between the life-sustaining and life-improving merits of treatment. Procedures and treatments that reduce the patient's functional handicaps are ultimately both economically and morally sound.

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Medical
PROGRESS

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Algorithm for an Aggressive Diagnostic Approach to Obstructive Jaundice

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GIVEN A PATIENT with obstructive jaundice, one is obliged to answer two major questions. First, is intrahepatic cholestasis present or does an extrahepatic block exist? And second, if the obstruction is extrahepatic, what is the nature, location and extent of the lesion? Historical details, physical findings and laboratory results may point to one of the many causes of intrahepatic cholestasis (see Table 1).[1-19] More often, however, symptoms and findings are not definitive and liver function tests cannot discriminate intra- from extrahepatic cholestasis (see Table 2). The diagnostic options for the clinician cover a wide spectrum. On one end is the "conservative" approach of watchful waiting, while on the other hand is the "radical" approach of diagnostic laparotomy. For several reasons, neither extreme is entirely satisfactory:

- If intrahepatic cholestasis exists, watchful waiting may delay appropriate medical therapy and worsen the prognosis. In extrahepatic cholestasis, hepatocellular damage, secondary biliary cirrhosis, gallstone fistula, deterioration of coagulation and nutrition or ascending cholangitis may ensue while the clinician charts the course of the bilirubin and enzymes. If malignant obstruction exists, the chances for resection or cure may be missed.
- Although a diagnostic laparotomy can disclose whether or not an extrahepatic block exists, there are pitfalls to this approach. Patients with primarily hepatocellular disease present a formidable operative risk and generally tolerate a surgical procedure and its attendant anesthesia poorly.

Over the past few years several authors have accepted the premise that the optimal diagnostic workup should establish or exclude extrahepatic cholestasis, and if extrahepatic cholestasis exists, the nature and extent of the process should be made known to the surgeon before laparotomy, so that he can plan the most effective operative approach.[20-24]

Physicians are now faced with a staggering list of diagnostic studies. Some are simple with little or no morbidity but offer low accuracy; other methods are complicated and expensive and present varying degrees of morbidity and even mortality. The question is which procedure or procedures should be employed and in what sequence.

We will present a brief summary of these techniques, but will stress certain of the newer ones, and conclude by suggesting an algorithm (that is, a method for problem solving, using branching logic) which we believe will allow the clinician to solve most problems of obstructive jaundice quickly, efficiently and with the maximum degree of safety.

Diagnostic Studies

Many methods have been proposed, to be employed either alone or in various combinations (see Table 3).[25-54] Each of the approaches or combinations has its advantages and disadvan-

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TABLE 1.—*Causes of Intrahepatic Cholestasis*

Fatty Liver[1]
Viral hepatitis[2]
Alcoholic hepatitis[3]
Chronic active hepatitis; post-necrotic cirrhosis[4]
Drugs—Intravenously administered tetracycline,[5] chlorpromazine hydrochloride (Thorazine®),[6] oral contraceptives,[7] methyl testosterone,[8] halothane,[9] azathioprine[10]
Lymphoma[11]
Primary biliary cirrhosis[12]
Cholestasis of pregnancy (3rd trimester)[13]
Benign, recurrent intrahepatic cholestasis[14]
Post-operative jaundice (anoxia, transfusions, etc.)[15]
Sclerosing cholangitis[16]
Sclerosing bile duct carcinoma[17]
Dubin Johnson, Rotor syndromes[18]
Pericholangitis[19]

TABLE 2.—*Causes of Extrahepatic Obstruction*

Very common (25 to 35 percent)
Choledocholithiasis
Carcinoma, head of pancreas

Common (5 to 10 percent)
Carcinoma of common duct
Stricture, common duct
Ampullary carcinoma

Uncommon (1 to 5 percent)
Chronic pancreatitis
Sclerosing cholangitis
Lymphoma
Metastatic carcinoma
Primary liver cell carcinoma

Rare (less than 1 percent)
Post-bulbar ulcer
Hepatic artery aneurysm
Choledochal cyst
Biliary atresia
Duodenal diverticulum

TABLE 3.—*Diagnostic Approaches to Obstructive Jaundice*

Procedure
1. Liver biopsy (percutaneous, transhepatic)[25]
2. Steroid response test[26,27]
3. Hypotonic duodenography (HD)[28,29]
4. Rose Bengal liver scan (RBS)[30]
5. Intravenous cholangiography (IC)[31]
6. Drip infusion cholangiography[32-34]
7. Selective visceral angiography (SVA)[35]
8. Percutaneous transhepatic cholangiography (PTC)[36-38]
9. Transjugular cholangiography (TJC)[39]
10. Endoscopic retrograde cholangiopancreatography (ERCP)[40-43]
11. Operative cholangiography[44,45]

Diagnostic Combinations
1. Peritoneoscopy and liver biopsy[46]
2. Peritoneoscopic cholangiography[47]
3. Secretion test (ST) and duodenal cytology (DC) and HD[48]
4. Open transhepatic cholangiography (OTC) and open liver biopsy (OLB) plus omento-portography (OP)[49]
5. PTC and SVA[50,51]
6. SVA and direct portography[52]
7. PTC and RBS[53]
8. TJC and transjugular liver biopsy (TJB) and SVA[54]
9. Algorithm

tages. Percutaneous liver biopsy cannot always discriminate intra- from extrahepatic cholestasis. Even if lesions pathognomonic for an extrahepatic obstruction are noted (hepatic bile lakes, bile infarcts), the cause and site of the block remain undisclosed. Furthermore, there is a risk of bile peritonitis or hemoperitoneum in patients with high grade obstruction or associated abnormalities of coagulation or both. The clinical response to a large dose of steroids is not valid, because of too many false positives.[26,27] Hypotonic duodenography (HD)[28,29] can be helpful in pancreatic carcinoma and ampullary lesions but is not as useful in choledocholithiasis, proximal biliary tract and hepatic lesions. The separation of pancreatitis from a pancreatic neoplasm can be most difficult. The Rose Bengal (RBS) liver scan[30] may suggest extrahepatic obstruction but usually cannot determine its cause.

Intravenous cholangiography[31] often results in poor visualization in patients with liver disease. Bile ducts are opacified in fewer than 10 percent of patents whose serum bilirubin is greater than 3 mg per 100 ml. Some authors favor the drip infusion cholangiogram, claiming better visualization at higher bilirubin levels and fewer side effects.[32,33] These results are disputed by others.[34] Selective visceral angiography (SVA)[35] has advantages and will be discussed in detail. Percutaneous transhepatic cholangiography (PTC)[36-38] is diagnostic in about 90 percent of patients with extrahepatic obstruction. However, the normal (nondilated) biliary tract can only be opacified in 10 to 40 percent of cases. Its relative ease and accessibility have made it a widely used procedure. Because of the risk of bile peritonitis and hemoperitoneum, it should be done in a patient prepared for a surgical procedure.

Transjugular cholangiography (TJC)[39] and endoscopic retrograde cholangiopancreatography (ERCP)[40-43] offer several advantages over PTC although they are more difficult to do and not so widely available. These will both be discussed in some detail. Operative cholangiography[43,44]

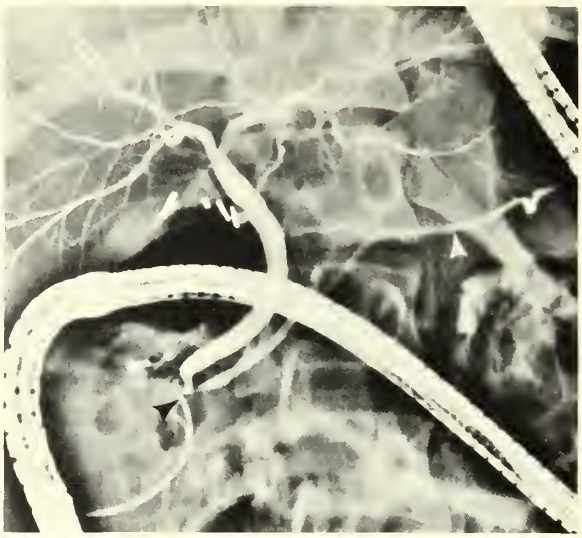

Figure 1.—Normal biliary and pancreatic ducts. Endoscopic retrograde cholangiopancreatography (ERCP) shows the side viewing endoscope in the descending duodenum, the cannula tip in the papilla of Vater (black arrow) and simultaneous filling of the biliary and pancreatic ducts. White arrow points to the main pancreatic duct in the tail of the pancreas. Surgical clips are from cholecystectomy.

Figure 2.—Biliary calculi. A hugely dilated common bile duct containing multiple calculi (black arrows) is shown with endoscopic retrograde cholangiopancreatography. White arrow points to normal pancreatic duct.

TABLE 4.—*Comparison of Cholangiographic Techniques**

	Intravenous Cholangiography	*Percutaneous Cholangiography*	*Transjugular Cholangiography*	*Transduodenal Cholangiography (ERCP)*
Difficulty	†	2†	4†	4†
Degree of Obstruction	Low (serum bilirubin less than 3 mg per 100 ml)	High only	High only	High; low; none
Ducts Visualized	Common bile duct	Common bile duct Hepatic	Common bile duct Hepatic	Common bile duct, hepatic and/or pancreatic duct
Papillary and Duodenal Biopsy and Cytology	No	No	No	Possible
Contraindication	Sensitivity to contrast	Same as for liver biopsy	Cholangitis; coagulopathy	Acute pancreatitis, hepatitis-B antigenemia†
Complications	Anaphylaxis	Bile peritonitis, hemorrhage	Sepsis, hemorrhage	Pancreatitis, sepsis

*Modified from Katon et al: Am J Dig Dis 19:303, 1974
†A relative contraindication reflecting problems in instrument sterlization.

often is diagnostic but high detail films may be difficult to obtain in the radiology department. If all cholangiograms were done in this way, the nonobstructed patients would be unnecessarily subjected to general anesthesia and its attendant risks. In terms of the diagnostic combinations, peritoneoscopy and liver biopsy[46] may document the cause of intrahepatic cholestasis and are particularly helpful in ruling in or out hepatic neoplasm. Peritoneoscopic cholangiography[47] offers the possibility of biliary tract visualization but is not generally available. The triad of secretin test (ST), duodenal cytology (DC) and HD[48] was effective in pancreatic and ampullary lesions but not as helpful in choledocholithiasis and bile duct neoplasms. The "minilaparotomy" with combined open transhepatic cholangiography (OTC), open liver biopsy (OLB) and omento-portography (OP)[49] was diagnostic in all 50 patients in one series. The absence of further reports of this com-

Figure 3.—Cancer of the pancreas. Endoscopic retrograde cholangiopancreatography shows the cannula in the common bile duct (open arrow). There is a short irregular narrowed segment above which the biliary tract is greatly dilated.

Figure 4.—Postsurgical stricture. A dilated common hepatic duct (open black arrow) above a severe stenosis (solid white arrows) is shown using endoscopic retrograde cholangiopancreatography. Normal pancreatic duct (solid black arrow). Contrast material outlines the duodenum to the left of the ducts.

bination since 1971 suggests reluctance of other centers to attempt it.

We have had extensive experience in the use of three newer procedures, ERCP, SVA and TJC, at the University of Oregon Medical School for the diagnosis of obstructive jaundice. It should be noted that these are technically demanding procedures requiring experienced personnel and delicate, costly equipment. They are time-consuming and relatively expensive for the patient. Despite these facts, the unique advantages of each allow for an aggressive but relatively safe diagnostic approach to the jaundiced patient.

Endoscopic Retrograde Cholangiopancreatography (ERCP)

ERCP refers to the placement of a lateral-viewing fiberduodenoscope into the mid-descending duodenum, cannulation of the papilla of Vater and subsequent opacification of the biliary or pancreatic ductal systems or both. While remaining a technically difficult procedure, it continues to gain in popularity and should soon be available in most medical centers. Technical aspects have been amply discussed in the literature.[40-43,55,56] ERCP is used for investigation of biliary and pancreatic diseases of various types; however, its most clear-cut indication is the investigation of patients with obstructive jaundice.

ERCP offers several advantages over other cholangiographic techniques (Table 4). First, the duodenum and papilla of Vater can be inspected under direct vision, and biopsy and brushing cytology may occasionally diagnose a pancreatic or papillary neoplasm. Second, visualization of the biliary tract does *not* depend on hepatic function as in intravenous cholangiography nor on biliary obstruction and consequent dilatation of intrahepatic ducts as in the percutaneous transhepatic or transjugular approach. Excellent biliary opacification can be obtained in the normal (Figure 1) or partially obstructed biliary tract, as well as in cases with pronounced obstruction (Figures 2, 3, 4). Third, a retrograde pancreatogram is often obtained, and may give additional clues as to the nature or cause of obstruction such as chronic pancreatitis or carcinoma of the head of the pancreas. Fourth, and probably most important, neither the peritoneum nor the liver capsule is punctured, eliminating the risks of bile peritonitis and hemoperitoneum, as in the percutaneous transhepatic route. Finally, ERCP allows the collection of cytological[57] specimens or fluid for carcinoembryonic antigen[58] study from both ducts.

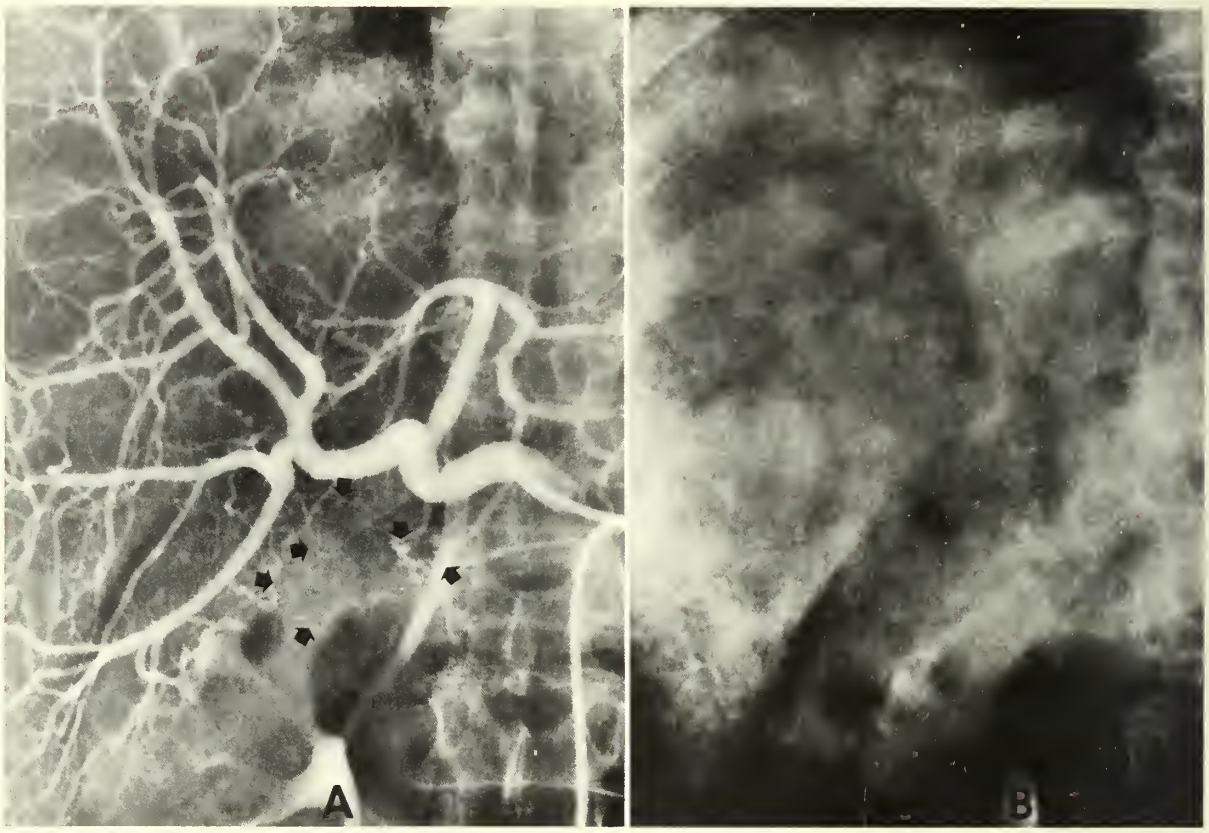

Figure 5.—Carcinoma of the hepatic duct. **A,** arterial phase of the selective hepatic arteriogram shows tumor invasion of small arteries in hepatic hilum (arrows). **B,** parenchymal phase of the selective hepatic arteriogram shows irregular ribbon-shaped translucencies throughout the liver.

ERCP does have diagnostic limitations and, at best, has been diagnostic in only 70 to 83 percent[40-43] of jaundiced patients. Failure may be due to inability to locate the papilla (3 to 5 percent), but more often it is due to opacification only of a pancreatic duct without biliary filling (20 to 25 percent). Complications may occur with ERCP, most commonly cholangitis and pancreatitis. In four large series[41-43] of ERCP in jaundiced patients plus 68 patients in our present series there were 28 complications (6.4 percent) in 436 patients. Half of these were listed as cholangitis with sepsis, and all appeared in the first 24 to 48 hours after cannulation and only in patients with extrahepatic obstruction. Other complications included fever (6), pancreatitis (3) and aspiration pneumonia (2). There was no mortality in this series of patients, although Ammon has reported fatal necrotizing pancreatitis after filling a pancreatic pseudocyst.[59]

It is prudent to advise a broad spectrum antibiotic, such as ampicillin prophylactically 24 hours before and after cannulation in jaundiced patients. If choledocholithiasis or other benign obstructive disease is documented, decompression operation within 24 hours is advisable. A probable exception to this rule is obstruction secondary to chronic pancreatitis, which may lessen as pancreatic inflammation subsides. On the other hand, if neoplasm is strongly suspected, further investigation is indicated (see Figure 10), but antibiotic coverage should be continued until biliary decompression is accomplished.

Due to its diagnostic advantages and relative safety, we prefer ERCP as the primary diagnostic procedure in patients with high-grade jaundice of uncertain cause.

Selective Visceral Angiography (SVA)

SVA can provide detailed information about individual organs and systems and is of great value in the diagnosis of obstructive jaundice.[20,51,60] By revealing the size, intrinsic vasculature and changes in the liver, pancreas, gallbladder, portal circulation and intrahepatic bile ducts, SVA helps to differentiate extrahepatic from intrahepatic jaundice,

Figure 6.—Carcinoma of the head of the pancreas. Selective celiac arteriogram reveals irregularity and narrowing of the celiac, hepatic, splenic and pancreatic arteries (arrows) and enlarged gallbladder delineated by optic artery branches (arrowheads).

Figure 7.—Carcinoma of the head of the pancreas. Transjugular cholangiogram shows severe stenosis of the distal common bile duct (arrows) with enlargement of the biliary system.

localized from diffuse processes and non-neoplastic lesions from tumors. By determining the extent of a tumor and the secondary involvement of surrounding organs and vessels, it contributes to evaluation of tumor operability (see Figures 5, 6, 8). SVA also allows for determining the probability of successful transjugular cholangiography by indicating the size of intrahepatic ducts on the capilliary-venous hepatogram. It increases the safety of TJC by showing anatomy of liver, position of gallbladder and hypervascular structures as tumors or aneurysms, or as fluid-filled masses such as cysts or abcesses.

SVA is a relatively low-risk procedure. Local complication at the site of catheter introduction may occur, but we have experienced occlusion of the femoral artery requiring thrombectomy in less than 0.3 percent of patients.[60] Selective angiography of the celiac and superior mesenteric arteries is a standard examination. Direct hepatic artery injection provides better visualization of the liver and gallbladder. For detailed evaluation of the pancreas, direct injections into the gastroduodenal, inferior pancreaticoduodenal or dorsal pancreatic arteries give the best result.[61]

Obstructive jaundice with cholestasis and enlarged intrahepatic ducts, whatever its cause, exhibits a typical pattern on the hepatic angiogram. The intrahepatic arteries, particularly the middle-sized branches, and the liver parenchyma reveal irregular, ribbon-shaped translucencies corresponding to enlarged hepatic ducts (see Figure 5).[62] The gallbladder is best visualized in the capillary phase of angiography and its size is a helpful indicator of the site of obstruction (see Figure 6).

The diagnostic accuracy of SVA depends on the type of pathology. It is high (90 to 96 percent) in diffuse hepatic disease such as hepatitis and cirrhosis, intrahepatic tumors, particularly hepatomas and vascular metastases, and pancreatic carcinomas (see Figures 6, 8).[63-68] Biliary carcinomas, particularly those of extrahepatic ducts and the duodenal papilla, cause vascular changes relatively late when they invade the neighboring vessels (see Figure 5).[69] In the early stage, they often present only by the nonspecific enlargement of the biliary system. A chronically inflamed, enlarged common bile duct, particularly due to impacted stones, may also show typical angiographic changes. Table 5 reviews the angiographic findings in many of the lesions associated with obstructive jaundice.

Due to its wide range of diagnostic information

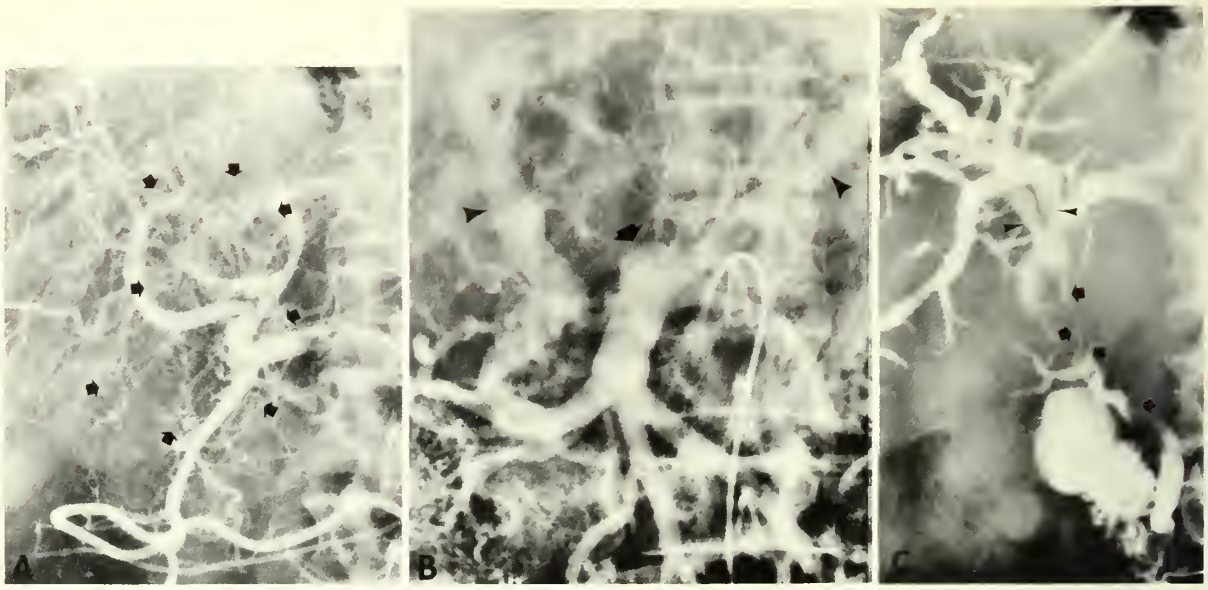

Figure 8.—Liver carcinoma extending into the porta hepatic. **A**, selective hepatic arteriogram reveals extensive tumor vascularity in the central part of the liver and subhepatic area (arrows). **B**, venous phase of the superior mesenteric arteriogram shows occlusion of the portal vein (arrow) and filling of enlarged hepatopetal and hepatofugal collaterals (arrowheads). **C**, transjugular cholangiogram reveals tight irregular stenosis of the common bile duct and hepatic duct (arrows) and displacement and narrowing of the central portion of the intrahepatic ducts (arrowheads).

TABLE 5.—*Scheme of Typical Angiographic Findings of Diseases Causing Obstructive Jaundice*

Disease	*Main Angio Findings*
Acute and subacute hepatitis	Increased hepatic vascularity and irregular outlines of smaller arteries; dense capillary phase with small hypervascular foci
Chronic hepatitis	Narrowing and stretching of medium-sized hepatic arteries, poor filling of peripheral branches, homogeneous capillary phase
Cirrhosis	Enlargement of hepatic artery and its major intrahepatic branches, cork-screwing of medium-sized branches, poor filling of peripheral branches, hypervascular foci in capillary phase with regeneration, signs of portal hypertension, collateral circulation, varices
Hepatoma	Hypervascular mass with bizarre tumor vessels, vascular lakes, and arteriovenous shunts, displacement and invasion of surrounding hepatic arteries, invasion and occlusion of portal vein branches
Hypervascular liver metastases (kidney, islet-cell, colon, breast, carcinoid carcinoma)	Multifocal tumor neovascularity, displacement of surrounding hepatic branches, multiple dense foci in capillary phase
Hypovascular liver metastases (lung, esophagus, stomach, pancreas carcinoma)	Deformity, displacement, invasion and occlusion of hepatic branches, multiple rounded defects in capillary phase
Pancreatic carcinoma	Tumor invasion and occlusion of pancreatic and peripancreatic arteries and portal vein and its branches, enlargement of gallbladder and intrahepatic ducts
Ampullary carcinoma	Enlargement of gallbladder and intrahepatic ducts (early finding), invasion of duodenal and pancreatic arteries (later finding)
Gallbladder carcinoma	Mild tumor neovascularity, invasion and occlusion of cystic artery branches (early finding), invasion of neighboring hepatic arteries (late finding)
Bile duct carcinoma	Enlargement of intrahepatic bile ducts and occasionally of gallbladder (early finding), tumor invasion of surrounding arteries (late finding)
Bile duct stones	Enlargement of intrahepatic ducts and occasionally of gallbladder (early finding), hypervascularity of the common bile duct with chronic inflammation.

Figure 9.—Carcinoma of the hepatic duct. Transjugular cholangiogram shows tight irregular stenosis of the hepatic duct (arrows), enlargement of intrahepatic ducts and normal-sized gallbladder, cystic and common bile ducts.

and low risk, SVA is done in patients in whom ERCP is nondiagnostic or shows changes consistent with tumor to demonstrate its extent and evaluate its operability.

Transjugular Cholangiography (TJC) and Liver Biospy (TJB)

In the transjugular approach to transhepatic cholangiography and liver biopsy, a catheter needle system is introduced into the internal jugular vein and advanced down through the right atrium into an hepatic vein. The needle is then used to enter and inject the intrahepatic biliary system and to aspirate a liver specimen for biopsy (see Figures 7 through 9).[39,54,70] Safety is one of the important advantages of this approach over the standard transperitoneal technique. By eliminating the necessity for traversing the peritoneal cavity and puncturing the liver capsule, there is virtually no risk of hemoperitoneum and both procedures can be done safely, even in patients with hemocoagulation defects. Bile peritonitis is also avoided so there is no need for surgeons to stand by for possible immediate operation. In the published series none of these complications occurred.[39,54,70] Occasional occurrence of fever and sepsis after cholangiography reported in Hanafee's initial experience[70] has been reduced with the prophylactic use of antibiotics,[39] and we have not observed either.[54] TJC, however, is contraindicated in patients with acute suppurative cholangitis.

The success rate of TJC is related to the dilatation of intrahepatic ducts and ranges between 88 and 93 percent when intrahepatic ducts are enlarged.[39,54] The transjugular approach allows several safe puncture attempts from different hepatic veins and in different directions; thus the inability to enter the biliary tract is strong evidence against its dilatation. The success rate of liver biopsy in our series is 89 percent, and most failures were caused by not obtaining an adequate specimen from a hard cirrhotic liver.[54]

Performance of concurrent studies is another advantage of the transjugular approach. The recording of wedged hepatic vein pressure gives information about portal pressure, and the performance of free and wedged hepatic venography helps in detailed evaluation of liver pathology and the flow pattern of the portal circulation.[71]

We reserve TJC for patients in whom the biliary system cannot be visualized by ERCP. TJB is done occasionally in combination with TJC or as the principal goal in patients with diffuse liver disease but with coagulation defects, ascites or other contraindications to the percutaneous transhepatic approach.

Discussion: Algorithm

Over the last three years more than 100 patients with obstructive jaundice have been evaluated at the University of Oregon Medical School. This clinical experience, coupled with use of newer diagnostic techniques, permits a systematic approach to an individual patient. The algorithm (Figure 10) seems particularly well suited to this clinical situation. Given a patient with jaundice of the obstructive variety, the first question should be, Is this an acute surgical emergency? In the event of high, relapsing spiking fevers, pronounced leukocytosis and pronounced hepatic tenderness, the patient may be in overt or impending shock secondary to Gram-negative bacteremia. In this situation, with severe ascending and possibly suppurative cholangitis, the only course of action should be immediate surgical decompression after

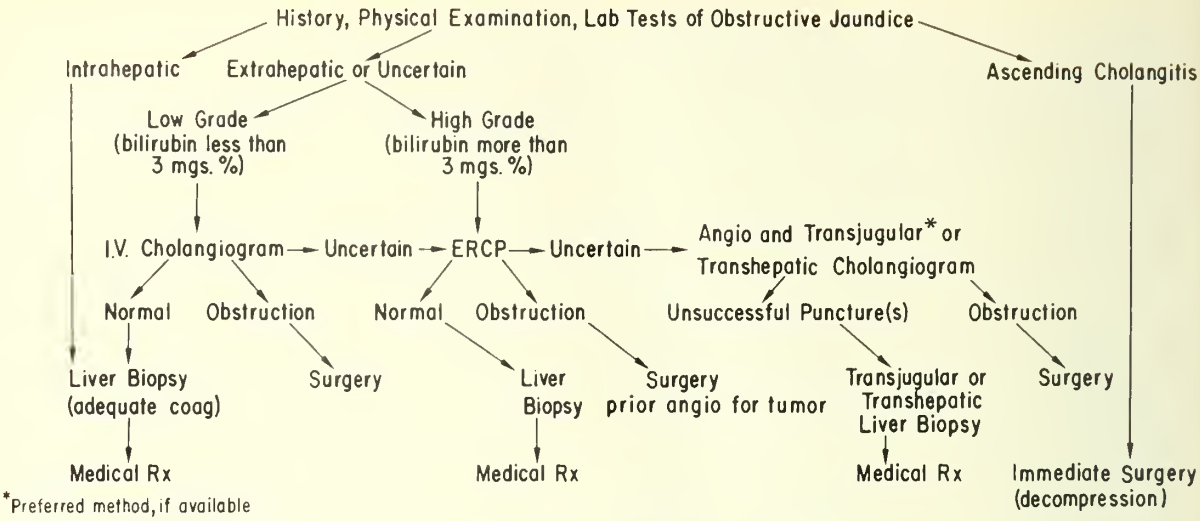

Figure 10.—Algorithm for an aggressive diagnostic study of obstructive jaundice.

stabilizing the patient with expansion of plasma volume and administering antibiotics.

The other end of the spectrum is a patient who clearly has intrahepatic cholestasis, such as an alcoholic with the signs and symptoms of acute alcoholic hepatitis, a patient with viral hepatitis and a positive hepatitis-associated antigen who has prolonged cholestatic features or a patient with drug-induced cholestasis with fever and eosinophilia. In these patients, biopsy can usually be done safely regardless of the level of the bilirubin because extrahepatic obstruction clearly is not present and they are not at risk for development of bile peritonitis. In the event of ascites or inadequate coagulation the transjugular route to liver biopsy has been used.

However, after initial evaluation, in many patients there is obstructive jaundice of uncertain origin or there clearly seems to be extrahepatic obstruction. The main concern is to visualize the biliary tract. If the jaundice is of low grade intensity (bilirubin less than 3 mg per 100 ml), we usually begin with the intravenous cholangiogram (IC). If the findings from this are clearly normal, a liver biopsy usually is done and the appropriate medical therapy may be instituted. On the other hand, if choledocholithiasis is diagnosed on IC, surgical operation should be done without delay. If the diagnosis remains uncertain after the IC or if the patient has high-grade biliary obstruction (bilirubin greater than 3 mg per 100 ml), then we proceed directly to ERCP. In our institution this has been successful 75 percent of the time regardless of whether the ducts are dilated or nondilated. Because of the relatively low complication rate and the ability to visualize a nonobstructed biliary tract, this is the procedure of choice in these patients. If the biliary tract is normal at ERCP, then a liver biopsy is done. If obstruction is due to calculus or benign stricture, surgical operation should be undertaken within 24 hours. However, when a neoplastic obstruction is strongly suggested by the ERCP, we obtain SVA before operation. This gives additional information such as the full extent of the lesion, the presence or absence of hepatic metastases and the vascular anatomy of the pancreas and liver.

If the diagnosis remains uncertain after ERCP, as it does in approximately 25 percent of the patients, then the combination of visceral angiography and transjugular cholangiography is employed. Visceral angiography provides information on hepatic enlargement, metastases, bile duct dilatation and pancreatic vascular supply which allows for discrimination between pancreatic inflammation and carcinoma. The transjugular cholangiogram follows (under antibiotic coverage), and the diagnosis and location of the extrahepatic obstruction usually (88 to 93 percent of cases), becomes obvious. The patient is then referred for surgical operation to be done within 24 to 48 hours.

If transjugular cholangiography is unsuccessful, the radiologist usually proceeds with a transjugular liver biopsy, accomplished at the same sitting. The transjugular cholangiography and transjugular liver biopsy—which are available only at a limited number of institutions—may be replaced, but with higher risk, by percutaneous transhepatic cholangiography or transhepatic liver biopsy or both.

In the case of suspected primary biliary cirrhosis, is the finding of a positive antimitochondrial antibody enough to establish a diagnosis? Since extrahepatic obstruction can be associated with a positive antimitochondrial antibody (3 to 7 percent) and since results of a liver biopsy in primary biliary cirrhosis may not be definitive, the biliary tract should be visualized before being satisfied with this diagnosis.

The use of these newer invasive but relatively safe procedures has enabled us to employ an aggressive approach in the diagnosis of obstructive jaundice. In most cases an accurate diagnosis is arrived at in three or four hospital days. Appropriate medical or surgical therapy can then be initiated without delay. Needless surgical operation in intrahepatic cholestasis is prevented, and when an operation is done it is almost always with full knowledge of the nature and extent of the extrahepatic lesion. This algorithm is not meant to be the definitive workup for all institutions nor will it necessarily remain static at our institution. As newer techniques emerge and modifications of existing ones are introduced, the algorithm will be modified.

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Specialty Conference

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Refer to: O'Rourke RA, Crawford MH, Johnson AD, et al: Prolapsing mitral valve leaflet syndrome—University of California, San Diego (Specialty Conference). West J Med 122:217-231, Mar 1975

Prolapsing Mitral Valve Leaflet Syndrome

DR. ROBERT A. O'ROURKE:* *Midsystolic clicks and late systolic murmurs, previously thought to be innocent and extracardiac or pericardial in origin,[1-6] have recently been shown to be a part of a common and highly variable clinical syndrome caused by a functional abnormality of the mitral valve.[7-12] Since 1961 when Reid attributed both the midsystolic click and the late systolic murmur to mitral valve regurgitation,[13] there has been considerable information obtained concerning the clinical, echocardiographic, cineangiographic and pathologic findings in this syndrome. Recent data indicate that prolapse of the mitral valve leaflets, variously called the click-murmur syndrome, the billowing mitral valve leaflet syndrome and the floppy valve syndrome, may occur in as much as 5 to 10 percent of the population.[14-16] Dr. Michael Crawford will begin this specialty conference by discussing the clinical presentation of patients with mitral valve prolapse.*

DR. MICHAEL H. CRAWFORD:† The clinical presentation of the prolapsing mitral valve leaflet syndrome is quite diverse and except for a preponderance of women, the typical patient cannot be stereotyped. The variability of the clinical findings in these patients is related to the underlying causes, to the extent of the mitral valve abnormality and to other unidentified physiologic factors. The following discussion will describe the symptoms and signs of the prolapsing mitral valve leaflet syndrome and their underlying physiologic mechanisms.

Most of the patients with mitral valve prolapse are probably asymptomatic and clinical findings are detected by auscultation during a physical examination for other reasons. Most of the reported patients in the literature, however, had one or more symptoms which might have been caused by the mitral valve abnormality. The most common complaints are palpitation, chest pain, dyspnea and fatigue. The frequently vague nature of these and other complaints has provoked some to consider them functional or psychoneurotic symptoms.[10]

The symptom of palpitation associated with the prolapsed mitral valve syndrome is clearly related to the presence of arrhythmias. Frequent atrial and ventricular premature beats, paroxysmal supraventricular tachyarrhythmias and ventricular tachycardia have been reported in patients with this syndrome.[17] Arrhythmias are occasionally present on the resting electrocardiogram (ECG), but more often can be induced or aggravated by physical exertion. However, the presence of ar-

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rhythmias during exercise is not related to the presence of ischemic (ST-T wave) ECG changes.[18]

Despite the frequency of arrhythmias detected in these patients, syncope is an unusual complaint. However, the increased incidence of sudden death reported by some authors in patients with the familial form of this syndrome has been attributed to arrhythmias,[19] and the overall reported incidence of sudden death in the literature has been estimated to be 1.2 percent.[17] Therefore, some authors recommend routine exercise testing of all persons with this syndrome to detect dangerous arrhythmias.[20]

The chest pain associated with this syndrome is particularly difficult to evaluate. Although it may be substernal, it is often prolonged and poorly related to exertion. It rarely resembles typical angina pectoris, but it can be incapacitating. Ischemic ECG changes have been reported at rest and during exercise but they do not correlate with the presence or the absence of chest pain.[18] Recent work at our institution has shown that the chest pain in this syndrome can be reproduced by selectively elevating systemic arterial pressure and hence left ventricular systolic pressure with intravenously administered phenylephrine.[21] The increased left ventricular systolic pressure would exert more force on the billowing mitral valve leaflets and increase papillary muscle tension during systole. If the increased tension in the papillary muscles interfered with regional blood supply or augumented regional oxygen demands excessively or both, pain could be produced. However, there is currently no documentation of abnormal levels of systemic arterial pressure in ambulatory patients with spontaneous pain. Thus, the precise mechanism of the chest pain in this syndrome remains speculative and it must be distinguished from the chest pain of ischemic heart disease.

Complaints of dyspnea and fatigue are common but are usually not progressive and are not associated with signs of congestive heart failure. Some patients describe typical episodes of hyperventilation. Objective evaluation of these complaints has shown no consistent reduction in exercise tolerance.[17]

The most common physical finding in this syndrome is the midsystolic click. The click is a high-pitched sound sometimes described as snapping or popping, which can vary considerably in intensity and timing from beat to beat. A single midsystolic click is the most common finding, but two, three or four are not unusual. Most often they occur 0.14 seconds or more after the first heart sound and if there are two or more clicks, they are usually .02 to .04 seconds apart. The clicks are thought to be generated by the sudden tensing of the mitral valve apparatus when the prolapsing mitral leaflet reaches its maximum posterior excursion.[8] They are best heard at the apex and lower sternal border near the mitral valve. Such high frequency midsystolic sounds have also been described in patients with pneumothorax, left ventricular aneurysms or aneurysms of the interventricular septum.[1,22] Midsystolic clicks must also be differentiated from systolic ejection sounds which arise from the semilunar valves or great vessels. Ejection sounds are best heard at the base of the heart, occur early in systole, are almost always single and usually do not vary appreciably in timing—as mentioned later.

The midsystolic click is often followed by a high-pitched late systolic murmur, which usually is heard best at the apex with the patient in the left lateral decubitus position. It is caused by blood regurgitating through the prolapsed mitral valve leaflet into the left atrium. The murmur is crescendo-decrescendo, peaking at the time of maximum mitral valve leaflet prolapse in late systole. Sometimes the murmur begins before the click and occasionally extends through the aortic component of the second sound.[23] The timing of the murmur is variable, and in some patients it is the only physical finding in this syndrome. When this

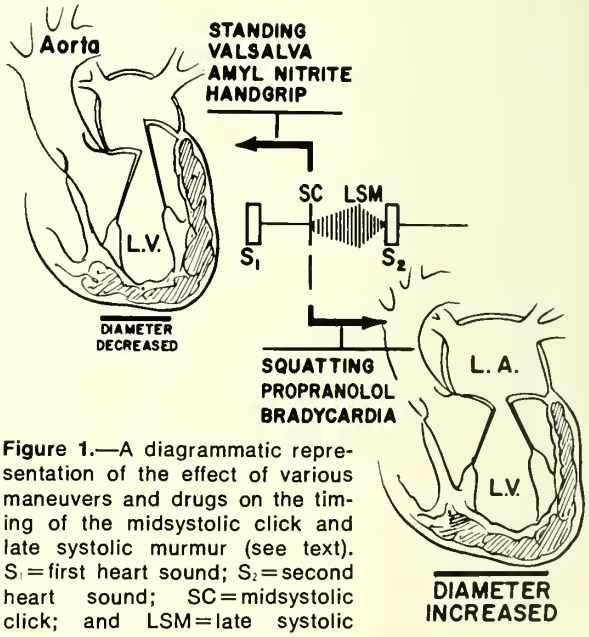

Figure 1.—A diagrammatic representation of the effect of various maneuvers and drugs on the timing of the midsystolic click and late systolic murmur (see text). S_1 = first heart sound; S_2 = second heart sound; SC = midsystolic click; and LSM = late systolic murmur.

occurs it must be distinguished from other systolic murmurs, especially those that peak late in systole, such as the murmur of papillary muscle dysfunction.

The midsystolic click and late systolic murmur associated with prolapse of one or both mitral valve leaflets are best identified by their characteristic responses to various maneuvers (Figure 1). Interventions which decrease left ventricular end-diastolic volume exaggerate chordal redundancy and increase the propensity for mitral leaflet prolapse. Therefore, prolapse occurs earlier in systole and the click and murmur move toward the first heart sound. The simplest way to decrease end-diastolic volume in the ambulatory patient is to have the subject sit or stand. Other methods include the Valsalva maneuver, amyl nitrate inhalation or increasing the heart rate with mild, submaximal handgrip exercise. With these provocative maneuvers, the murmur may become holosystolic and the click may move closer to the first sound, often disappearing within it or resembling an early systolic ejection sound. Conversely, interventions which increase left ventricular end-diastolic volume diminish the propensity for the mitral valve leaflets to prolapse and the click-murmur complex moves later in systole and may even disappear if prolapse is abolished. The easiest bedside maneuver to increase end-diastolic volume is rapid squatting which augments venous return to the heart, increases systemic peripheral resistance by compressing the femoral arteries and causes reflex bradycardia. Any intervention that slows the heart rate, such as the administration of the beta-adrenergic blocking drug propranolol, also will increase left ventricular end-diastolic volume. Thus, the end-diastolic left ventricular volume seems to be a major determinant of the onset of mitral valve prolapse and hence, the timing of the systolic click and murmur.

The intensity of the click is dependent on systolic left ventricular pressure and contractile force. Hence, with the Valsalva maneuver it becomes softer and with handgrip exercise it becomes louder. The intensity of the murmur varies with different maneuvers as does classical mitral regurgitation. Interventions which increase the intensity of the murmur, such as handgrip exercise, may also cause a honking or musical sound to occur during the murmur.[24] The response to amyl nitrate inhalation is usually biphasic. During the initial phase of vasodilatation after amyl nitrate inhalation, the murmur becomes softer, as does the murmur of rheumatic mitral regurgitation. Later, however, as reflex tachycardia develops, the murmur of mitral valve prolapse often increases as end-diastolic volume diminishes.

Certain variations in the findings described above tend to occur in patients with identifiable underlying heart diseases. The clicks described in some patients with rheumatic heart disease are lower pitched and do not change their timing predictably with the maneuvers outlined above. Also, the mitral regurgitant murmurs are more often pansystolic and frequently there are signs of associated mitral stenosis.[25] The clicks in patients with predominant ischemic heart disease can also be lower pitched. They seem to move appropriately with changes in ventricular volume but lack the spontaneous variation in timing seen in most patients with the prolapsed mitral leaflet syndrome.[26]

Other physical findings occur in these patients which may be related to the causes of the syndrome. Many patients without overt features of the Marfan syndrome have been found to have certain bony abnormalities, such as high-arched palate and chest and thoracic spine deformities.[27] Particular care should be taken to exclude associated atrial septal defect which has been reported to occur with increased frequency in patients with mitral valve prolapse. However, a late systolic click may mimic fixed splitting of the second heart sound and lead to the false impression of atrial septal defect.

The systolic murmur of mitral valve prolapse can usually be distinguished from other systolic murmurs by its response to the maneuvers described above. Idiopathic hypertrophic subaortic stenosis (IHSS), however, presents an especially challenging differential diagnosis. The systolic murmur due to left ventricular outflow obstruction resembles the murmur of mitral leaflet prolapse in many of its features and midsystolic clicks have occasionally been observed in patients with IHSS.[28] The murmur of IHSS may peak late in systole and it decreases in intensity and duration with squatting and increases with standing. However, isometric handgrip exercise usually decreases the intensity of the murmur of IHSS and the Valsalva maneuver *greatly* increases it, in contrast to the murmur of mitral leaflet prolapse. Also there is no early decrease in intensity of the murmur of IHSS with amyl nitrate inhalation as occurs with the murmur of mitral valve prolapse. However, the most consistent difference in the murmurs of mitral valve prolapse and IHSS is the

change in intensity that occurs in the cardiac cycle following a premature contraction, the murmur of subaortic stenosis increasing in duration and loudness and the murmur due to billowing mitral leaflets diminishing or remaining unchanged.

There is some evidence from the physical findings that the degree of mitral valve apparatus involvement may be progressive. Isolated clicks are more common in children, the complex of click and late systolic murmur is common in young adults and older patients tend to have prominent mitral regurgitant murmurs.[29] Several postulates have been entertained to explain this progression. One is that in many of these patients, subacute bacterial endocarditis develops which further impairs the valvular apparatus leading to more prominent mitral regurgitation. Another explanation is that the cumulative stress to the mitral apparatus resulting from initial chordal redundancy leads to further abnormalities in the structure of the mitral leaflets and even the adjacent ventricular wall (mitral regurgitation begets mitral regurgitation). Furthermore, rupture of the chordae tendineae, in the absence of endocarditis, occurs in patients with the prolapsed mitral valve leaflet syndrome.[30] However, the true incidence of progression of this lesion from mild mitral valve prolapse to severe mitral regurgitation is not well defined.

Findings on the electrocardiogram and vectorcardiogram have been reported to be abnormal in a high percentage of patients with the prolapsing mitral valve leaflet syndrome, even if patients with obvious coronary artery disease are excluded.[31] The most common finding is T-wave inversion in the inferior leads (II, III, AVF) and occasionally V_5 and V_6 (Figure 2). Rarely, Q waves and ST segment elevation are seen in these same leads.[32] Large "U" waves in the limb leads and a prolonged QT interval have also been reported. The arrhythmias seen in this syndrome do not seem to be related to these ECG abnormalities.[18,20] Various causes for these ECG abnormalities have been postulated such as (1) ischemia of the left ventricular wall adjacent to the papillary muscles that are under increased tension, (2) hyperventilation, (3) compression of the circumflex coronary artery by the billowing posterior leaflet and (4) the existence of a cardiomyopathy. However, these theories are unproven and the mechanism of the ECG abnormalities and arrhythmias remains obscure, as does the reason why they are seen only in some patients.

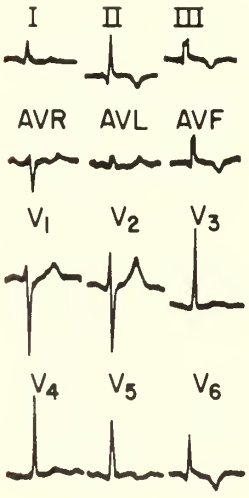

Figure 2.—Schematic representation of an electrocardiogram pattern seen in patients with the prolapsing mitral valve leaflet syndrome.

The variable clinical presentation of the prolapsing mitral valve leaflet syndrome can mimic many other cardiac diseases and make diagnosis difficult. Usually, the history, physical examination and electrocardiogram are sufficient, but some patients will require further procedures (discussed later) to confirm or exclude the diagnosis. Patients with a history of palpitation, syncope or sudden death in the family and those in whom arrhythmias are noted on physical examination or resting ECG should have an exercise ECG test.

DR. O'ROURKE: *The prolapsing mitral valve leaflet syndrome has been observed in association with a variety of clinical disorders including the Marfan syndrome, other connective tissue diseases, coronary artery disease and atrial septal defects. It often occurs in several members of the same family. As just described, the clinical manifestations of mitral valve disease are quite variable, with there being only an isolated systolic click in some patients and evidence of severe mitral regurgitation in others. Dr. Allen Johnson will discuss the structural abnormalities of the mitral valve and its supporting structures in patients with mitral valve prolapse and the possible causes of this syndrome.*

DR. ALLEN D. JOHNSON:* The phenomenon of prolapsing mitral valve leaflets, having been recognized only relatively recently, now encompasses a number of causes and pathophysiologic mechanisms. Originally felt to represent sounds of extra-

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TABLE 1.—*Pathophysiologic Mechanisms of Mitral Leaflet Prolapse*

1. Mitral Leaflet Abnormalities
   (a) Excessive or redundant leaflet tissue
   (b) Myxomatous degeneration
2. Chordae tendinae abnormalities
   (a) Shortened, fibrotic
   (b) Elongated, redundant
   (c) Ruptured
3. Papillary muscle disorders
   (a) Abnormal orientation
   (b) Inadequate shortening
4. Abnormalities of left ventricular contraction
   (a) Localized
   (b) Diffuse
5. Abnormal function of the mitral annulus

cardiac origin, the characteristic clicks and murmurs identified with this syndrome have now been associated with various forms of dysfunction of the mitral valve apparatus. As reviewed by Perloff and Roberts,[33] the functional anatomy of the mitral valve includes: the left atrium, the mitral valve annulus, the mitral leaflets, the chordae tendinae, the papillary muscles and the left ventricular wall—particularly the regions of insertion of the papillary muscles. Disordered anatomy or function of any of these structures may cause the mitral valve to function abnormally, resulting in mitral regurgitation. Conceptually, abnormal function of any portion of the mitral apparatus might permit excessive posterior excursion of the mitral valve leaflet(s) during systole, and it is no surprise, therefore, that the prolapsing mitral valve leaflet syndrome has been associated with abnormalities of each of the various structures mentioned.

While the definite diagnosis of prolapse of the mitral valve leaflet(s) requires anatomic documentation of a specific type of abnormal mitral valve motion by cineangiographic or echocardiographic techniques (as mentioned later), many of the clinical features are so typical as to suggest the proper diagnosis. Thus, as discussed by Dr. Crawford, the auscultatory findings of systolic clicks and systolic murmurs, a history of atypical chest pain, an abnormal resting electrocardiogram and recurrent arrhythmias encountered in this clinical syndrome often have as a common denominator angiographic or echocardiographic evidence of mitral valve leaflet prolapse.

In reviewing the various causes identified and mechanisms postulated as causes of the billowing mitral valve leaflet syndrome, each of the various elements of the mitral valve apparatus must be considered (Table 1). Excessive or redundant mitral leaflet tissue has been identified in a number of cases, and can involve the anterior leaflet or the posterior leaflet—or portions of either leaflet. Redundant leaflet tissue is commonly found to be involved with myxomatous degeneration and is a frequent finding in patients who have the typical features of the Marfan syndrome or of Erdheim's cystic medial necrosis.[34] However, myxomatous degeneration can be confined to the mitral valve leaflets without other clinical or pathologic manifestations of disease.[35,36] Various abnormalities of the chordae tendinae have been specifically identified in this syndrome. If chordae to either leaflet, or portions of a single leaflet, are unequally involved with a pathologic process, inadequate coaptation of the mitral leaflets during left ventricular systole might occur. In this regard, short, attenuated chordae as well as elongated, redundant chordae tendinae have been identified in the billowing mitral leaflet syndrome. Chordal fibrosis, as occurs in patients with rheumatic mitral disease, has been associated with myxomatous mitral valve leaflets.[8,35,37,38] In this regard, systolic clicks with late systolic murmurs have been described in patients with acute rheumatic fever. Thin, elongated chordae have been identified as well in patients with mitral valve prolapse; whether the decrease in thickness is a primary or secondary abnormality remains conjectural.[23,35,38] Frank rupture of chordae tendinae can also result in mitral leaflet prolapse.[38]

Dysfunction of the papillary muscles, particularly in the setting of coronary artery disease, has often been associated with auscultatory and angiographic evidence of mitral regurgitation. The systolic murmur in this setting is also unlike that of rheumatic mitral regurgitation since it is mid- or late systolic in timing. Recently, the clinical features associated with prolapse of the mitral valve leaflets have been described in patients with coronary artery disease, giving rise to the hypothesis that dysfunction of the papillary muscles can result in prolapse of the mitral valve leaflets during systole.[39] While systolic clicks or atypical mid to late systolic murmurs or both have been well-documented in patients with ischemic heart disease, angiographic evidence of mitral leaflet systolic prolapse in this setting is not frequent. Considering the relative frequency of each of these two disorders, ischemic heart disease and prolapse of the mitral leaflets, the existence of both dis-

orders in the same patient could represent a chance occurrence. In patients without evidence of coronary artery disease, in whom prolapse of the mitral leaflets has been shown, abnormal orientation or inadequate shortening of the papillary muscles has been identified, and could be responsible for the abnormal leaflet position during systole.

Abnormalities of left ventricular contraction have been described in patients with systolic clicks with or without evidence of associated billowing of the mitral valve leaflets. The contraction abnormalities described can be categorized as either localized or diffuse. Localized or regional disorders of the left ventricular contraction described in this syndrome include decreased systolic shortening of the inflow area of the left ventricle, increased or decreased contraction of the midportion of the left ventricle, shortening of the base to apex left ventricular axis, and diminished or exaggerated contraction of the posterior left ventricular wall.[40-44] It is unclear whether abnormal tension on the mitral valve leaflets, chordae tendinae and papillary muscles is responsible for the abnormal left ventricular contraction pattern, or whether the abnormal left ventricular contraction pattern alters the geometric relation of the papillary muscle and suspensory apparatus of the mitral valve leaflet—allowing it to prolapse with resulting mitral regurgitation.

Diffuse abnormalities of left ventricular function have also been described in patients with billowing mitral leaflets. Mitral valve prolapse has occasionally been noted in patients with hypertrophic obstructive cardiomyopathy, in whom the anterior mitral leaflet is displaced anteriorly during systole and the posterior leaflet sometimes prolapses into the left atrium.[45] In nonobstructive, hypertrophic cardiomyopathy, mitral leaflet prolapse has been documented, particularly when there is a pronounced decrease in left ventricular end-systolic volume.[45] As will be discussed later in this conference, Gulotta and associates have described diffusely abnormal left ventricular contraction patterns in some patients with billowing mitral valve leaflets.[46]

Abnormal function of the mitral annulus has also been suggested as a possible cause of mitral leaflet prolapse, and billowing of the mitral leaflets has been observed in patients with mitral annulus calcification and associated angiographic evidence of decreased systolic contraction of the mitral annulus.[47]

Patients with secundum atrial septal defects have a higher than expected incidence of mitral valve prolapse; the pathophysiologic explanation for this association is unclear, although mitral leaflet prolapse is only rarely noted in other forms of congenital heart disease.[48]

The familial incidence of systolic clicks and mid to late systolic murmurs has been noted since the original descriptions of this syndrome.[24,49,50] Whether the familial occurrence of billowing mitral valve leaflets includes some or all of the above postulated mechanisms is not certain at present.

DR. O'ROURKE: *As has been mentioned, the clinical presentation of patients with the prolapsing mitral valve leaflet syndrome is quite variable and this syndrome often occurs in association with other cardiac disorders. It would therefore be desirable to have a sensitive, accurate, noninvasive technique for evaluating patients with suspected mitral valve prolapse. Fortunately, echocardiography when properly done is a reliable method for diagnosing prolapse of one or both mitral valve leaflets. Dr. Robert Davidson will describe the ultrasound technique and echocardiographic findings in patients with this syndrome.*

DR. ROBERT M. DAVIDSON:* Echocardiography has become an increasingly important clinical tool in the diagnosis of a variety of cardiac disorders. There is no better example than that of mitral valve prolapse, in which an echocardiogram is frequently diagnostic of anterior or posterior mitral leaflet billowing into the left atrium. In order to understand the specific abnormality in this condition, it is useful to review the motion of the normal mitral valve echogram as illustrated in Figure 3. The anterior leaflet of the mitral valve is easily recorded and has a characteristic "M" shape. Various points on the echogram have been labeled A through F by convention and correspond to the position of this structure at specific times in the cardiac cycle. Following the onset of left ventricular diastole at Point D, the mitral valve opens and the anterior leaflet reaches its maximum anterior position at Point E. The mitral valve then partially closes and Point F is the end of partial closure. It then opens further with atrial contraction at Point A, and begins to close before the onset of left ventricular contraction which occurs at Point B. The valve is closed completely at Point C, and then

*Assistant Professor of Medicine (In Residence).

during systole gradually moves anteriorly back to Point D. This anterior motion from C to D is probably due to emptying of the left ventricle during systole. It is this systolic portion of the mitral valve echo, the C to D segment, upon which the following discussion will be centered.

Depending upon the exact transducer position, various portions of the posterior mitral valve leaflet are also commonly detected. The movements of this leaflet are approximately opposite in direction to those of the anterior mitral valve leaflet during diastole. Shortly after the onset of systole (Point C) both leaflets come together and stay in apposition until Point D, at which time valve opening begins.

The abnormal echocardiographic appearance of the mitral valve in the syndrome of mitral valve prolapse was first recognized in 1970 by Shah and Gramiak who described two types of abnormal systolic motion.[51] In the first type, which has become recognized as most characteristic of this syndrome, the early systolic motion is normal, but there is an abrupt posterior displacement of one or both mitral valve leaflets in mid to late systole,

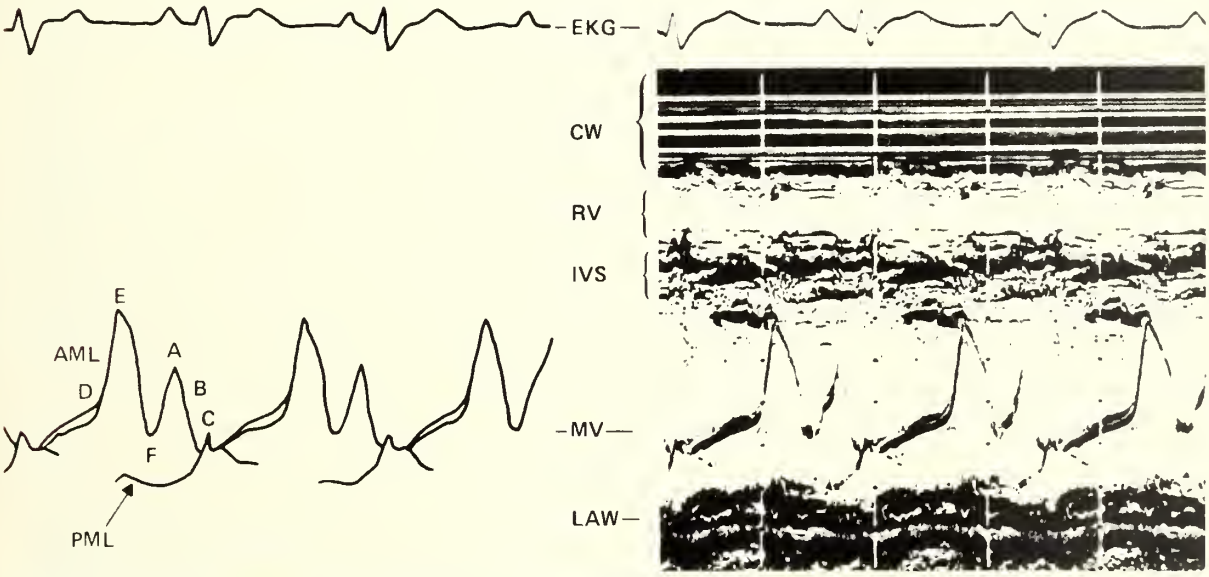

Figure 3.—Normal mitral valve echogram. The recorded echo is illustrated on the right and a schematic tracing of the mitral valve motion on the left. CW=chest wall; RV=right ventricle; IVS=interventricular septum; MV=mitral valve; AML=anterior mitral leaflet; PML=posterior mitral leaflet; and LAW=left atrial wall. The letters A through F correspond to the letters described in the text.

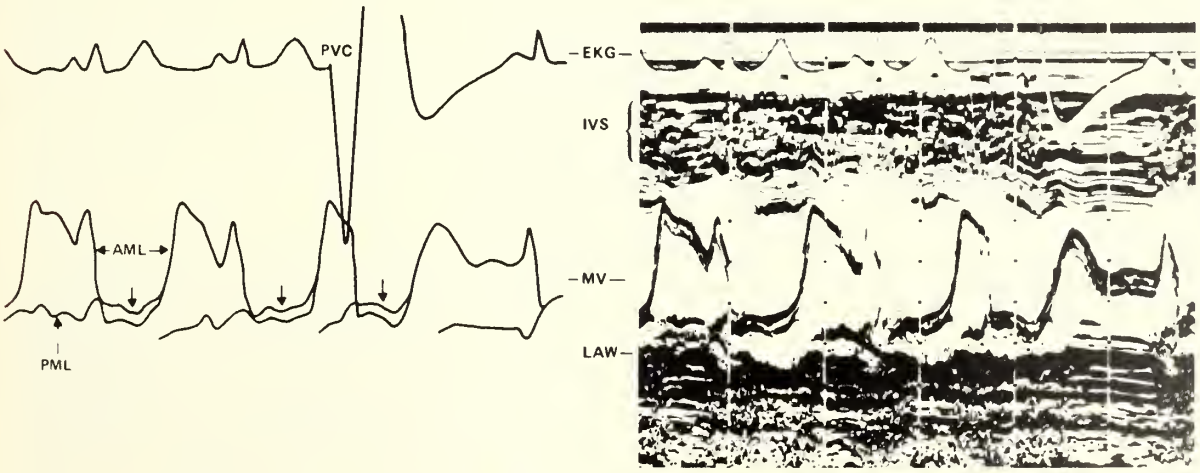

Figure 4.—Echocardiogram from a patient with mitral valve prolapse. The areas of posterior displacement of both mitral leaflets are illustrated by arrows. This abnormal motion is exaggerated following a premature ventricular contraction.

as illustrated in Figure 4. This ultrasound pattern is frequently observed in patients with a midsystolic click and late systolic murmur,[49-53] and has not been seen in any other condition. The onset of this posterior mitral leaflet displacement occurs very shortly after the systolic click,[52] and occurs earlier in systole and lasts longer when the subject is given amyl nitrate to inhale.[53] During the posterior displacement of the mitral leaflets, there is usually some separation between the anterior and posterior leaflets. Although this separation was initially felt to correlate with the presence and degree of mitral regurgitation, subsequent studies have not substantiated this hypothesis.[54,55]

Many patients with this syndrome, including patients with mitral valve prolapse who have atypical physical findings, have a second type of abnormal echocardiogram.[55] In these patients, the mitral valve echogram shows a gradual and smooth posterior motion of the mitral leaflets which begins shortly after the onset of systole and is followed by a gradual anterior motion back to the C Point (Figure 5). This gradual posterior and then anterior systolic motion gives the echogram a smooth hammock-like appearance and has been referred to as the pansystolic type of abnormality. In addition, there are frequently multiple *abnormally* moving parallel echoes recorded during systole in patients with mitral valve prolapse which are probably a result of the echo beam passing through the folds of a redundant mitral valve.[54,55] This finding is often seen in patients with mitral valve prolapse due to ruptured chordae tendineae,[56] as well as in patients with mitral valve prolapse and either a holosystolic murmur, multiple systolic clicks or no abnormal physical findings.[54,55] There is an overlap in physical findings between patients with the two main types of abnormal echocardiograms, and the echocardiographic pattern cannot be reliably predicted from the physical examination. The explanation for the two different types of echocardiograms seen in mitral valve prolapse is not clear at this time, and needs to be more fully evaluated with combined angiographic and echocardiographic studies. The absence of either of these two types of abnormal echocardiograms at rest or during interventions in patients with mitral valve prolapse is uncommon and the presence of a normal, carefully recorded mitral valve echogram makes this diagnosis less likely.

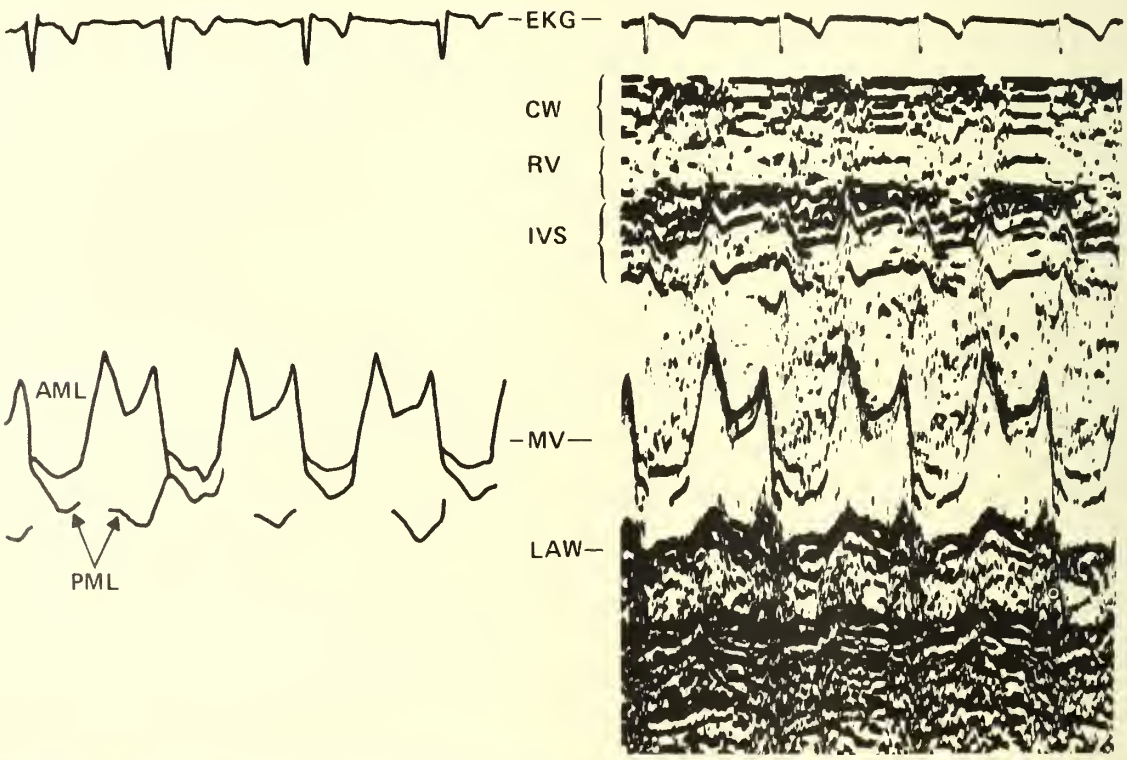

Figure 5—Pansystolic type of mitral valve prolapse. This shows the hammock or U-shaped abnormal type of systolic motion and two distinct separate echoes during systole, which represent the anterior and posterior leaflets.

Several precautions need to be taken, however, in obtaining and interpreting ultrasound recordings of the mitral valve in patients with suspected prolapse. Careful scanning of the mitral valve by tilting the transducer is necessary to identify this structure at all levels. Mitral valve prolapse should not be excluded unless this is done, and unless the posterior mitral valve leaflet is recorded. The best transducer angle for recording mitral valve prolapse is one in which the junction of the posterior left ventricular wall and posterior left atrial wall is seen behind the mitral valve echo.[57] When the posterior left ventricular wall, rather than the posterior left atrial wall, is recorded behind the mitral valve, the motion of the posterior mitral valve leaflet during systole is frequently obscured by the motion of the left ventricular wall. It is often desirable to place the transducer at an interspace lower than usual (fifth rather than fourth left intercostal space) and direct the transducer angle upward toward the left atrium to accomplish this.[59] Certain factors must be considered in order to avoid the incorrect ultrasound diagnosis of mitral valve prolapse. For example, a limited posterior motion of the mitral valve can be recorded at the beginning of systole in normal persons, lasting no more than 0.04 seconds.[54] This posterior displacement is small and is followed by a normal gradual anterior systolic motion, and should not be confused with the echo patterns seen in mitral valve prolapse.

Another normal finding which could be confused with mitral valve prolapse is the occasional recording of multiple mitral valve echoes during systole. These are parallel echoes which have *normal* anterior motion, are not widely separated, and are probably due to the ultrasound beam striking the mitral valve apparatus at an angle, thus passing through it at several points.[54] This multiplicity of echoes, however, is often exaggerated in mitral valve prolapse.

Another possible point of confusion is with an echocardiogram in idiopathic hypertrophic subaortic stenosis (IHSS), in which there is a characteristic abnormal systolic anterior motion of the mitral valve. Although this echo pattern consists of an initial exaggerated systolic motion of the anterior mitral valve leaflet followed by a posterior motion, the posterior motion in subaortic stenosis is anterior to the C Point while in mitral valve prolapse it is posterior to the C Point.[54] Moreover, amyl nitrate inhalation exaggerates the anterior motion in IHSS and exaggerates the posterior displacement in mitral valve prolapse.

Finally, in patients with low cardiac output there often are mitral valve echoes which show very little systolic anterior motion and can thus be confused with the pansystolic type of mitral valve echogram seen in the prolapsing mitral valve leaflet syndrome. However, in this type of echogram there is no posterior displacement of the mitral valve, only a limited amount of anterior motion.[54]

If these simple precautions are taken, echocardiography is extremely reliable in diagnosing mitral valve prolapse. Although the diagnosis can often be made on physical examination alone, physical findings can be variable, intermittent or absent in this syndrome and are less specific than the echocardiogram. Since patients with this syndrome are often symptomatic and are prone to complications, the echocardiogram provides a simple, safe and reliable method for making this important diagnosis.

DR. O'ROURKE: *Cardiac catheterization and left ventricular angiography are often unnecessary in patients with typical auscultatory and echocardiographic features of mitral valve prolapse. However, in some patients cardiac catheterization is necessary to evaluate the severity of the mitral valve regurgitation, the existence of left ventricular dysfunction, the presence or absence of coronary artery disease and the possibility of associated cardiac disease. Dr. Martin LeWinter will discuss the cardiac catheterization and angiographic findings in patients with billowing mitral valve leaflets.*

DR. MARTIN M. LEWINTER:* The diagnosis of mitral valve prolapse generally can be made by the presence of the typical auscultatory findings or mitral valve echocardiographic patterns described above, or both. Therefore, at present cardiac catheterization and left ventriculography are usually unnecessary to establish the diagnosis of mitral valve prolapse. Those patients in whom cardiac catherization is indicated generally fall into three groups: patients with chest pain in whom it is desirable to rule out the presence of coronary artery disease, patients who have clinical findings suggesting hemodynamically significant mitral regurgitation, and patients in whom some associated condition—such as atrial septal defect or hypertrophic cardiomyopathy—is suspected. As a cor-

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ollary, the recent literature describing hemodynamic and angiographic data in patients with this syndrome concerns more symptomatic patients and is probably not representative of the majority of patients with prolapsing mitral valve leaflets.

Most patients with a midsystolic click, late systolic murmur, or both, have normal resting intracardiac pressures at catheterization unless an associated cardiac abnormality is present. Barlow et al[23] reported that in 20 of 21 patients with this syndrome there were normal left ventricular pressures, the exception being a patient with associated hypertrophic cardiomyopathy. The left atrial pressure was normal in all seven patients in whom it was measured and in nine out of ten there were normal right heart pressures; there was an associated atrial septal defect in the one exception. Occasionally, in a patient with this syndrome there will be a mildly elevated left ventricular end-diastolic pressure[58,59] or an increase in the pulmonary artery wedge pressure associated with a prominent "v" wave on exercise.[10] Jeresaty[58] noted an exaggerated early diastolic dip followed by a rapid rise to a mid-diastolic plateau (square-root sign) in the right ventricular pressure recordings of two patients, in the left ventricular tracings of two other patients and in both right and left ventricular pressure tracings in one patient with this syndrome, this finding is similar to that seen in patients with restrictive pericardial or myocardial disease.

Patients with longer systolic murmurs or holosystolic murmurs tend to have more significant grades of mitral regurgitation.[60,61] In these persons, the hemodynamic findings are essentially identical to those with mitral regurgitation of other causes. Thus, variable degrees of elevation of the left ventricular end-diastolic pressure and pulmonary hypertension will be found and the "v" wave of the pulmonary artery wedge or directly obtained left atrial pressure may be prominent. In this group of patients the cardiac index may be depressed if mitral regurgitation is severe.

For descriptive purposes the angiographic find-

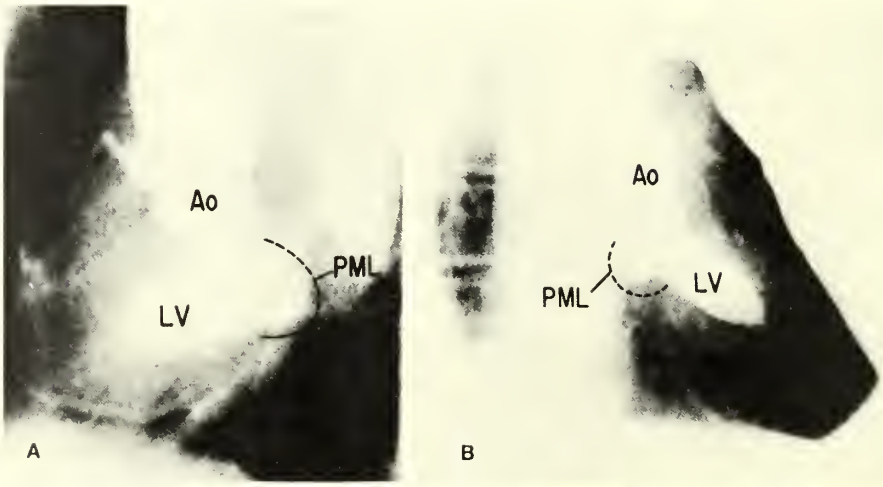

Figure 6.—Systolic frames from a left ventricular cineangiogram in the lateral **(A)** and anteroposterior **(B)** views showing prolapse of the posterior mitral valve leaflet (PML). LV=left ventricle; Ao=aorta.

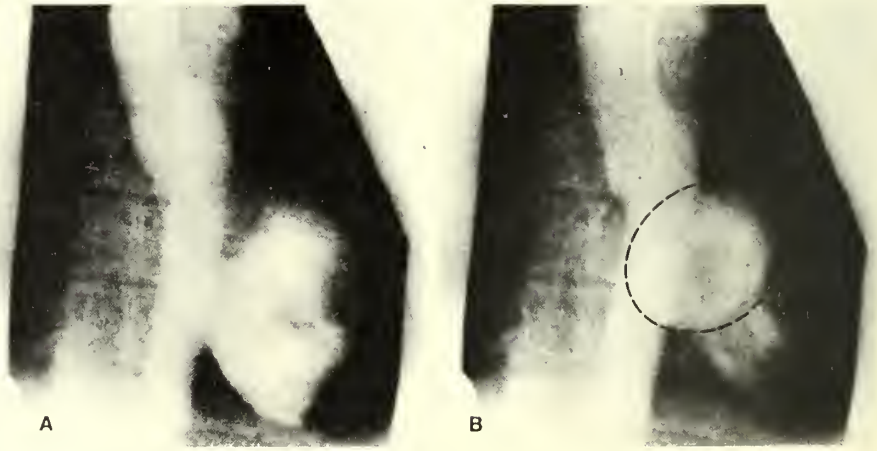

Figure 7.—End-diastolic **(A)** and end-systolic **(B)** frames of a left ventricular cineangiogram in the anteroposterior projection illustrating pronounced systolic prolapse of both leaflets and a "doughnut" deformity of the mitral valve (see text).

ings in patients with mitral valve prolapse can conveniently be divided into those due to the prolapsed mitral leaflets themselves and those relating to contraction abnormalities of the left ventricle. However, what relationship the two abnormalities have constitutes an important unsolved problem in patients with this syndrome.

Earlier angiographic studies were primarily concerned with documenting the presence of prolapse of the mitral valve leaflets into the left atrium during systole and correlating this observation with the auscultatory findings. In Barlow's original and expanded series of patients,[23,60] prolapse of the posterior leaflet was emphasized with little attention directed to anterior leaflet involvement. Patients with a midsystolic or late systolic click and no systolic murmur, often had no demonstrable mitral regurgitation.

Subsequent studies have further characterized and refined our understanding of the mitral valve abnormality. Linhart[58] and Jeresaty[62] emphasized the frequency of anterior leaflet involvement in addition to the posterior leaflet, while Bittar and Sosa[61] studied three patients in whom mitral regurgitation was so severe that valve replacement was required.

Typical examples of mitral leaflet prolapse from our laboratory are represented in Figures 6, 7 and 8. Figure 6 shows discrete prolapse of the posterior leaflet into the left atrium during systole. Of interest is the fact that this patient was admitted to the hospital with chest pain and a diagnosis of "crescendo angina." The heart sounds were distant and the diagnosis of prolapse was not suspected at the bedside. Findings on selective coronary arteriograms were normal in this patient. Figures 7 and 8 show notably reduplicated or "floppy" valves, with pronounced prolapse—probably of both leaflets—into the left atrium. In our experience this gross malformation of the mitral leaflets is present in a minority of patients.

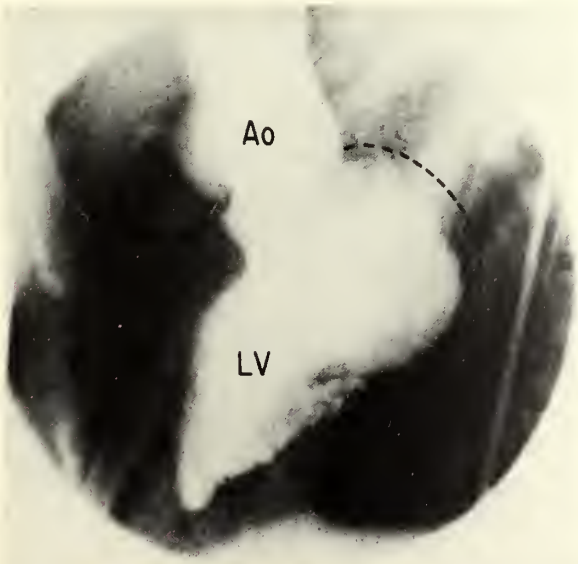

Figure 8.—A systolic left ventricular cine frame in the lateral projection showing severe prolapse of the mitral valve leaflets into the left atrium.

Ranganathan et al[63] have studied the morphology of the posterior mitral valve leaflet in postmortem specimens and in most cases found that it was a triscalloped structure; usually there was a large middle scallop surrounded by smaller anterolateral and posteromedial scallops. Using these morphologic findings, these authors[64] and Jeresaty[65] have attempted to refine further the angiographic interpretation of mitral valve prolapse with respect to the precise identification of which scallop or scallops of the posterior leaflet are involved and whether or not anterior leaflet prolapse is also present. According to the authors, the example shown in Figure 6 would most likely represent prolapse of the posteromedial and middle scallop of the posterior leaflet.

Another well-recognized angiographic pattern (Figure 7) is a doughnut-shaped mitral valve which is felt to represent generalized prolapse of both leaflets.

While Leachman[66] and Criley[8] identified abnormal systolic expansion of the mitral annulus in patients with mitral valve prolapse, Ehlers and associates[67] were the first to recognize contraction abnormalities of the left ventricle in association with the condition. Left ventriculography was done by these authors in a group of six females between the ages of 12 and 24—in all of whom there were typical auscultatory findings—and noted in each that the posteroinferior aspect of the left ventricle bulged into the cavity during systole producing, in the frontal projection, the appearance of a contraction ring. Subsequently, Liedtke and coworkers[44] analyzed mean circumferential fiber shortening rates in patients with prolapse at the proximal, middle and apical portions of the left ventricle and found significant reductions at the proximal level, near the mitral valve. Scampardonis et al[43] analyzed a large number of patients with prolapse and were able to identify five classes of abnormal left ventricular contraction patterns. These included posterior wall akinesis, decreased long axis shortening, an

inferior convexity with an anterior bulge (the ballerina foot), a contraction ring (the hourglass deformity), and left ventricular cavity obliteration. Finally, Gulotta et al[46] noted varying degrees of hypokinesis or dyskinesis (systolic bulging) of the anterolateral left ventricular wall in 20 of 22 patients undergoing left ventriculography. Schematic representations of some of these abnormal left ventricular contraction patterns are shown in Figure 9.

Thus, the spectrum of contraction abnormalities seen in patients with mital valve prolapse varies from subtle areas of diminished contractility to frank dyskinesis. Most of these contraction abnormalities are well localized and display a close anatomic and functional relationship to the mitral valve apparatus. What percentage of patients with prolapse exhibit such contraction abnormalities is not known at present, but several investigators have been sufficiently impressed with the frequency of angiographic abnormalities to suggest that the major problem in this group of patients may be a rather unusual segmental cardiomyopathy affecting the mitral valve apparatus and secondarily allowing prolapse. Since, in addition, there are many patients without angiographically detectable contraction abnormalities, it may ultimately become necessary to divide patients with mitral valve prolapse into a primary and secondary group, the latter containing those *with* contraction abnormalities affecting the valve apparatus. Clearly, this is an area which requires further careful study.

In 1973, Jeresaty[62] reviewed the available literature concerning coronary arteriograms in patients with the billowing leaflet syndrome. Findings on the coronary angiograms were normal in 118, mildly abnormal in two and significantly abnormal in two reported patients with mitral leaflet prolapse, excluding Cheng's series[68] which Jeresaty felt represented examples of coronary artery disease with papillary muscle dysfunction. In our experience also the findings on coronary arteriograms are usually normal in patients with billowing mitral leaflets. As indicated by Dr. Johnson, the occasional patient with mitral prolapse and coronary artery heart disease may represent the chance coexistence of two common entities. The available evidence would suggest that occlusive disease of the coronary arteries does not represent a part of the prolapsing mitral leaflet syndrome.

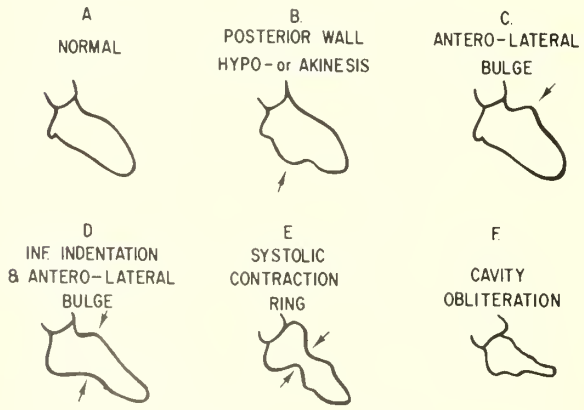

Figure 9.—A composite representation of several left ventricular contraction abnormalities described in association with mitral valve prolapse. Systolic frames from left ventriculograms obtained in the right anterior oblique projection are depicted.

A number of workers[10,29,69] have commented on the association of mitral valve prolapse with secundum atrial septal defect. Conversely, it has been suggested that 10 to 15 percent of patients with secundum atrial septal defect may have prolapsing mitral valve leaflets.[70] If this is the case, then the presence of a secundum atrial septal defect is an indication for at least a mitral valve echocardiogram in order to make a judgment with regard to endocarditis prophylaxis (mentioned later). Conversely, any suggestion of the presence of an atrial septal defect in a patient with prolapse necessitates ruling out a left to right shunt and may be viewed as an indication for right heart catheterization.

Another possibly associated condition which may be documented at cardiac catheterization is that of hypertrophic cardiomyopathy. There have been isolated case reports of this association in the literature[23] and Scampardonis[43] recognized a group of patients with angiographic evidence of left ventricular cavity obliteration during systole. What significance this apparent association has is not clear at present.

Finally, mention must be made of tricuspid valve leaflet prolapse in association with mitral valve prolapse, a surprisingly high incidence of which was noted by Scampardonis[43] in his series of patients undergoing both left and right ventriculography. This finding requires further verification by others.

DR. O'ROURKE: *The mitral regurgitation in patients with the prolapsing mitral valve leaflet syndrome is usually mild and does not warrant mitral*

valve replacement. However, the incidence of progression to severe mitral regurgitation and the occurrence rate of ruptured chordae tendinae remain unknown.

The treatment of patients with mitral valve prolapse is directed toward the prevention of bacterial endocarditis, the relief of atypical chest pain and the prevention of cardiac arrhythmias. Dr. Karliner will discuss the role of medical therapy in patients with this syndrome.

DR. JOEL S. KARLINER:* Many patients with the prolapsing mitral valve leaflet syndrome report chest discomfort that sometimes resembles angina pectoris. More often, however, the precordial pain is atypical in nature; it tends to be prolonged, inconsistently related to exertion and only occasionally relieved by nitroglycerin. Coronary arteriograms in such patients usually have not shown significant occlusive disease.[40,46] The origin of the atypical chest pain is obscure. In addition to atherosclerotic heart disease,[26] it has been ascribed to compression of the left circumflex coronary artery,[23,71] interference with the papillary muscle blood supply[27] and psychological factors.[10] As mentioned by Dr. Crawford, our own data indicate that an imbalance between myocardial oxygen supply and demand may play an important role in the pathogenesis of symptoms in these patients.[21]

Because of the resemblance of the chest pain to the discomfort experienced by patients with ischemic heart disease and the possibility that the pain may be related to alterations in myocardial oxygen demand, beta-adrenergic blockade has been used by a number of investigators with varying success. Sloman and his colleagues reported that propranolol (120 mg daily) controlled the pain in three and produced improvement in two patients, but caused no relief in three other patients.[72] Others have proposed that propranolol should be used in the treatment of atypical chest pain in patients with this syndrome,[71,73] and our own experience has indicated that the incidence and severity of precordial discomfort may be lessened or sometimes even abolished by propranolol therapy. However, in patients with hemodynamically and angiographically documented left ventricular dysfunction, propranolol may be ineffective in producing relief of symptoms.[16] Nevertheless, in patients who have atypical chest pain as a major complaint, the use of oral propranolol in a dose sufficient to produce adequate beta-adrenergic blockade (resting heart of less than 55 to 60 beats per minute) should be considered. It must be emphasized, however, that there are no published controlled studies of propranolol (or any other mode of therapy) in the treatment of chest pain accompanying this disorder, and that the favorable results reported are based largely upon subjective appraisals.

It is well known that life threatening arrhythmias may occur in patients with mitral valve prolapse. The precise incidence of these arrhythmias is uncertain, but they tend to be more common, as does sudden death, where there is a family history of the syndrome[29] or with patients in whom there is abnormal left ventricular wall motion.[40] Thus, Pocock and Barlow have advocated exercise testing of all patients with billowing mitral leaflets, since serious ventricular arrhythmias may be unmasked by this maneuver.[20] Of considerable interest is the high incidence of QT interval prolongation reported by several authors in patients without a family history of syncope or hereditary deafness.[10,40] In one remarkable patient with ballooning mitral leaflets and a prolonged QT interval who recovered from an initial bout of ventricular fibrillation but who died suddenly after hospital discharge, the coronary arteries and the conduction system were both grossly and microscopically normal.[19] Because of QT interval prolongation, propranolol and diphenylhydantoin—both of which tend to shorten the QT interval—were used to treat arrhythmias in these patients but without success. Pocock and Barlow successfully treated three patients with exercise-induced multifocal ventricular arrhythmias, one with diphenylhydantoin and two with propranolol.[20] Conversely, Gooch and his colleagues reported that none of four agents (digitalis, quinidine, propranolol and procainamide) was completely effective in abolishing exercise-induced arrhythmias in several patients.[40] Of considerable interest is the report of Gulotta and associates who observed two patients with mitral valve prolapse who developed complete heart block requiring permanent transvenous pacemaker implantation.[46]

The cause of the prolonged QT interval and the propensity to arrhythmias in these patients has not been adequately explained. It has been proposed that QT interval prolongation may be associated with unilateral autonomic imbalance

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(excess sympathetic tone) resulting in nonhomogeneous ventricular repolarization.[74] An intriguing possibility, as yet quite speculative, is that such autonomic imbalance may be related to the high incidence of psychiatric disorders observed in this syndrome. Indeed, Shapell and Gunn have reported that in four of six patients with billowing mitral leaflets and abnormal findings on a Minnesota Multi-Phasic Personality Inventory, serious ventricular arrhythmias occurred, including two episodes requiring cardiopulmonary resuscitation.[75]

Therefore, it is our policy that all patients with the "click-murmur" syndrome undergo exercise stress-testing, even though the incidence of serious arrhythmias unmasked by such a procedure may be low.[76] Furthermore, prolonged ambulatory ECG monitoring is recommended in all patients who complain of palpitations. Should serious arrhythmias be found, therapy with propranolol or other antiarrhythmic agents appears warranted. Under such circumstances, routine follow-up studies using both ambulatory ECG monitoring and exercise studies, are indicated.

A number of instances of bacterial endocarditis have been reported in patients with mitral valve prolapse, most of which have been due to streptococcus virdans.[14,29,52,72,77-79] Patients in whom there is a systolic click only and no murmur are not spared this complication.[80] In view of the clear association between bacterial endocarditis—especially the variety caused by streptococcus virdans—and billowing mitral leaflets, appropriate endocarditis antibiotic prophylaxis appears to be indicated for dental and surgical procedures in patients with this syndrome.

DR. O'ROURKE: In concluding this specialty conference I should like to emphasize that the prolapsing mitral valve leaflet syndrome is a common entity with protean manifestations including systolic murmurs, systolic clicks, atypical chest pain, abnormal resting electrocardiograms and resting or exercise-induced arrhythmias. Any combination or none of the clinical features may be associated with echocardiographic or angiocardiographic evidence of mitral valve prolapse.

The current definition of this syndrome most likely applies to several subsets of patients who differ in regard to the causes, pathogenesis and hemodynamic sequelae of their abnormal mitral valve function. Careful epidemiologic, clinical follow-up, hemodynamic and pathologic studies should improve our understanding of this common but complex clinical syndrome.

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Refer to: Brucellosis—Medical Staff Conference, University of California, San Francisco. West J Med 122:232-237, Mar 1975

Brucellosis

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Assistant Professor of Medicine, and H. David Watts, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, CA 94143.

DR. SMITH:* *Recently we have had two very interesting cases in the hospital representing brucellosis with osteomyelitis. The first summary will be given by Dr. Michael Jensen.*

DR. JENSEN:† The patient is a 68-year-old man who formerly worked as a renderer in a plant where animal carcasses were processed to tallow for soap. Approximately 28 years before admission he experienced recurrent fevers for which he was seen at Stanford where the diagnosis of brucellosis was made. He was treated with bed rest alone and underwent a spontaneous remission. In October 1972, an enlarged liver and elevated serum transaminase enzymes were noted. A liver biopsy was done and the resulting diagnosis was chronic active hepatitis. In January 1973, a Baker's cyst appeared behind the left knee and upon surgical incision it drained purulent material. Results of cultures were negative. Soon, the onset of recurrent afternoon fevers was noted. In June 1973, while the patient was playing golf, there was a sudden onset of neck pain and he was referred to the University of California. An extensive workup showed a normal leukocyte count with a very high sedimentation rate. Because initially there were thought to be meningeal signs, repeated lumbar punctures were done but findings were normal. The patient was started on steroids for a presumed vasculitis and clinically worsened. Subsequent x-ray films of the cervical spine showed a pronounced destructive process involving the fifth, sixth and seventh cervical vertebrae. One of six blood cultures, as well as the culture of material obtained at open biopsy of the fifth-sixth cervical disc space, showed the presence of Brucella suis. The brucella tube agglutinin (immunoglobulin M) titer was 1:640 and the brucella fluorescent antibody (immunoglobulin G) titer was 1:40. A 21-day course of ampicillin was given, which was followed by clearing of the toxicity and spinal tenderness. Fever cleared after one day of treatment. The patient was discharged with instructions to take ampicillin orally for six weeks. When seen in December 1973, the patient described the recent onset of mild left hip discomfort. Findings on x-ray films of the hip were unremarkable and repeat cervical spine films were unchanged. Orally administered ampicillin, 750 mg four times daily, was restarted and continued during the first five months of 1974. Recurrent afternoon fevers to 38°C (100.4°F) and increasing left hip discomfort were noted, and the patient was readmitted to hospital in May 1974.

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The medical history was remarkable for long-standing diabetes mellitus treated with insulin and diet. On physical examination, the patient appeared youthful and was wearing a cervical collar. A low-grade fever was noted. No lymph nodes were palpable. An atrial gallop was audible and the abdomen was flat. The liver was palpable two fingerbreadths below the right costal margin and the spleen tip was palpable at the left anterior axillary line. Neither was tender. The spine was not tender, but in the left hip there was moderate pain on motion without tenderness to direct palpation.

Neurological examination showed mild left triceps weakness, and the deep tendon reflexes in the upper extremities were mildly hyperactive. Knee jerks were normal, ankle jerks were absent bilaterally and there was a mild peripheral sensory loss. Laboratory data on admission included a hematocrit of 37 percent, a leukocyte count of 5,000 cells per cu mm with 56 percent polymorphonuclear cells, 25 percent lymphocytes, 12 monocytes, 5 eosinophils and 1 band form. Sedimentation rate was 46 mm per hour, serum glutamic oxaloacetic transaminase (SGOT) 102 international units (IU) per liter, alkaline phosphatase 105 IU per liter and hemaglobin antiglobulin was absent. Urinalysis showed 2 to 5 leukocytes per high-power field and 1 plus glucose. X-ray films showed moderate to severe distortion of the fifth, sixth and seventh cervical vertebrae with narrowing of the intervening disc spaces. There was narrowing of the left hip joint space and mild osteoporosis in the acetabulum.

Antibiotics were not administered during the hospital course, and daily afternoon temperature elevations were noted, usually between 37.6 and 38°C (99.7 and 100.4°F). Aspiration of the left hip under fluoroscopy yielded only a few drops of clear fluid without cells, and all cultures of the hip, as well as blood cultures, were negative. Oral administration of tetracycline, 500 mg four times daily, was begun, and there was subjective improvement and partial remission of fever.

DR. SMITH: *Thank you very much. This was a man who had a 25-year history of brucellosis with remission and then later recurrence of brucella osteomyelitis. We have a second patient whose history Dr. Jory Braun will summarize for us.*

DR. BRAUN:* The present illness of this 69-year-old white man, a former farm worker from the San Joaquin Valley, began 27 years before admission when recurrent right knee effusions first began, thought at that time to be the result of trauma. There were no subjective joint symptoms until nine months before admission when low-grade fevers, chills, night sweats, malaise, swelling in his right knee and pain in his right thigh began. In the month before admssion here, he was admitted to Scenic General Hospital in Modesto, where results of purified protein derivative of tuberculin (PPD) skin tests and tests for histoplasmosis, coccidioidomycosis and brucella agglutinins were negative. An x-ray film of the right femur showed intramedullary swelling with periosteal thickening. Cultures taken at incision and drainage of the right thigh were negative on two occasions. The patient was then transferred to the University of California Medical Center.

Upon admission here, the patient appeared chronically but not acutely ill. The temperature was 38°C (100.4°F). Significant physical findings were limited to the right lower extremity. There was a minimal right knee effusion, a fluctuant mass on the medial aspect of the right thigh and granulating wounds from the operative incisions. There was some atrophy of right calf muscles but no decreased range of motion in that leg. There was no peripheral lymphadenopathy and no hepatosplenomegaly. The hematocrit was 38 percent, leukocyte count 11,600 per cu mm with 81 percent polymorphonuclear leukocytes and sedimentation rate 60 mm per hour. Serum calcium and phosphorus, blood urea nitrogen (BUN) and results of urinalysis were within normal limits.

X-ray studies of the right leg showed changes consistent with chronic osteomyelitis of the right femur with a central radiolucency in the medullary cavity and dense calcifications probably due to sequestra. A sinogram showed intramedullary cavitation. On the first day of the patient's stay in hospital, the right thigh lesion was twice aspirated, but cultures from these procedures were negative. On the sixth hospital day, surgical exploration of the right femur was carried out. A sequestrectomy and window procedure were done, the marrow cavity was extensively opened and the operative incision was closed over irrigation tubes. On the 13th day at the University of California Medical Center, brucella agglutinins were found to be positive at 1:1260, and oral administration of tetracycline was begun, 500 mg every six hours. A culture taken during the surgical pro-

*Jory Braun, MD, Resident in Medicine.

cedure grew Brucella suis ten days later and streptomycin was added to the regimen. Subsequently, the right leg is no longer tender, and there has only been one episode of spontaneous drainage. Several febrile episodes have occurred lasting two to three days, but the patient has generally improved.

DR. SMITH: *Thank you very much. Last week in a Clinical Pathologic Conference here this patient was presented to Dr. Robert Roe from the San Francisco General Hospital, who without benefit of cultures or agglutinations made the correct diagnosis, much to his credit. This morning we are very pleased to have Dr. Stephen Cohen to discuss brucellosis and perhaps put specific emphasis on osteomyelitis.*

DR. COHEN:* This institution has a long and honorable historical association with brucellosis. The disease Malta fever was described over 100 years ago. Some 25 years later Bruce isolated the organism subsequently called Brucella melitensis from the spleen of a fatal case in Malta. Over the next 20 years the other major species of brucella, Brucella abortus and Brucella suis, were recovered from aborted animals. In 1920, the late Dr. Karl F. Meyer and Dr. Edward Shaw, now emeritus Professor of Pediatrics, united these organisms in the genus which they named Brucella. The history of brucellosis is well reviewed in the still classical monograph of Spink.[1]

Epidemiology

Brucella are very small Gram-negative rods which display moderate host specificity. B. melitensis is widely distributed particularly in the Mediterranean littoral in association with goats and sheep. B. abortus is associated with cattle and B. suis with swine. In the mid-1960's epidemic abortion of dogs, particularly of beagles, was traced to Brucella canis, a new species which may be related to B. suis. Other species of brucella are less important.

The last decades have seen pronounced changes in the epidemiology of brucellosis. Although those who work with the animals mentioned are at greatest risk of acquiring brucellosis, brucellosis is a hazard to every man where pasteurization of milk and cheese is not routine. B. abortus is the dominant species causing infection in most of the world, with B. suis being somewhat less prominent. B. melitensis classically causes the most severe disease but is not seen in this country except as it is imported—for example, by returnees from Spain, Italy or Mexico who typically have eaten unpasteurized dairy products. B. abortus was extremely common in this country 30 years ago, but has largely been eradicated through a very vigorous program conducted by the Department of Agriculture in conjunction with Department of Health, Education, and Welfare. The program included serological testing of cattle, slaughter of animals with evidence of infection with brucella, vaccination of range animals and pasteurization of milk. There were 6,500 cases of brucellosis in the United States in 1947 compared with about 200 cases per year at present. By comparison, the United Kingdom with a population one quarter that of ours has five times as many cases as we do. The United Kingdom has not undertaken a vigorous eradication program, and a substantial proportion of its population still drinks unpasteurized milk. In the United States, B. suis is the most common infecting organism, and brucella infection is an occupational disease.

The important epidemiological clue in both patients discussed today, even if the first was without a diagnosis of brucellosis 25 years ago, was the fact that they had worked in proximity to farm animals. As soon as the mention of farm, slaughterhouse or packinghouse is made, the diagnosis of brucellosis should cross the clinician's mind. It is important that he actively pursue the diagnosis because of potential technical difficulties in isolating or identifying the organism. Currently 75 percent of brucella infections in this country result from contact with swine, 75 percent of infections arise in slaughterhouse or packinghouse workers and about 70 percent of isolates are B. suis.[2] Most cases are reported from Iowa, California and Illinois. There has been a notable decrease in the number of cases from Texas—a state which has made a major attempt to eradicate the organism from swine. Swine remain an important source of brucellosis, partly because of the lack of commitment of the industry to its eradication—B. suis is not as serious an economic problem for the farmer as B. abortus is for the cattleman—and partly because serological tests are much less reliable in detecting infected swine. In California approximately 0.2 percent of swine studied were serologically positive. The organisms spread via aerosol and contact. Viable B. suis have been re-

*Stephen N. Cohen, MD, Associate Clinical Professor of Clinical Pathology and Laboratory Medicine, Medicine and Microbiology.

covered from the tops of fluorescent fixtures 20 feet above the floors of the slaughterhouse.

Brucellac enter the blood stream through mucous membranes or abrasions of the skin, then migrate to the lymphatics and the reticuloendothelial system. The incubation period of brucellosis varies from one to three weeks, but the initial infection is, in many cases, undetected or at least unrecognized. In our second case, we have no clear history of exposure or definite symptoms of an initial infection.

Clinical Presentation

There are four major clinical forms of brucellosis. The first, seen particularly with B. melitensis and B. abortus but also occasionally with B. suis, is an acute bacteremic infection resembling any other, and the blood cultures are readily positive. If the bacteremia is persistent and a high level of antibody develops, a diffuse nephritis may arise, perhaps on an immunologic basis.[3] In addition there may be focal abscesses in the kidney or other tissues. The bacteremic form of the disease is relatively short-lived.

Alternatively, an abacteremic, nonspecific illness may develop, resembling influenza or mononucleosis, or occasionally resembling poliomyelitis because of the profound limb weakness. This is the "serological" form of brucellosis in which the cultures are negative, but the patient has an appropriate epidemiological history and there is serological evidence of active infection.

Third, in about 15 percent of the cases there are focal complications, particularly with B. suis, as in our two patients today. These localizations may occur in any organ but about half of the time involve the skeleton, particularly the vertebral column.[4] Although spondylitis usually responds to medical treatment, bony involvement of other sites is particularly refractory and seems to require aggressive surgical drainage and debridement. Meningitis may arise from the spread of vertebral osteomyelitis. Endocarditis may also occur, and 15 years ago the question was raised whether calcific aortic stenosis might be a specific endocarditic result of brucellosis. Subsequently, it has appeared that such infection is simply coincidental and complicates a preexisting calcified valve. Splenic infection may give rise not only to characteristic calcifications, but to hypersplenism.

Finally, infection may persist—as in our first patient—for many years as a latent infection following an initial bout of brucellosis. Possibly a small abscess in the skeletal system or an intracellular focus in the reticuloendothelial system is reactivated.

In addition to its varied clinical manifestations, brucella organisms are unusual in that they are one of the few pathogens for which a specific biochemical determinant of disease has been found.[5] Brucella infection of goats, cattle and sows leads to placentitis and abortion. This localization seems to correlate with the normal presence of erythritol in the placentas but not in other tissues of these animals. Erythritol is a four-carbon sugar which brucella metabolize in preference to glucose. The correlation with erythritol is not complete, because the canine placenta does not contain erythritol but can develop a brucella placentitis.

Diagnostic Procedures

The diagnosis may come from a biopsy specimen of the involved tissues showing granulomata with or without caseation (Figure 1). Caseation is unusual, but when found, is usually associated with B. suis. X-ray studies may show a classical wagon-wheel calcium deposit in the spleen, but most patients do not have this finding.

The brucellergen skin test, used for a long time

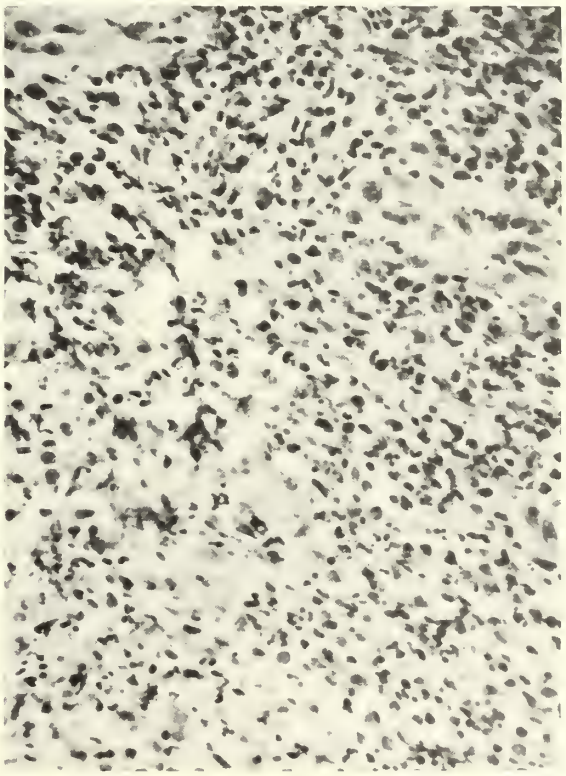

Figure 1.—Granulomatous inflammatory response in biopsy specimen from fifth cervical vertebra, Case 1.

TABLE 1.—*Serodiagnosis of Brucellosis*

Status of Infection	*Agglutination (IgM)*	*Complement-Fixation (IgG)*
Prior infection, not active	+	−
Following skin test or repeated exposure in patient with inactive infection	±	±
Active disease, acute or chonic .	±	+

in the diagnosis of brucellosis, is unreliable and, furthermore, like the tuberculin test, usually remains positive following the initial infection. Uncritical use of the skin test has resulted in an erroneous diagnosis of active brucellosis in many previously infected but recovered persons with neurasthenic syndromes. Like the histoplasmin skin test, the brucella skin test will induce a rise in serological titer, and may further mislead one if serum is not drawn first. For these reasons the skin test has fallen into disfavor[6] and the antigen is no longer available in the United States.

The most useful diagnostic tests for brucellosis are serologic,[7] but it is important to keep in mind that Gram-negative organisms such as brucella give a different serological progression of response from that which we normally expect. In most infections, initially formed immunoglobulin M (IgM) antibodies are replaced in turn by immunoglobulin G (IgG) antibodies, which persist for life. Usually, then, the presence of IgM antibody reflects active or recent infection, whereas the presence of IgG alone suggests remote infection. In contrast, following an infection with Escherichia coli, Salmonella typhosa or brucella, the usual early IgM antibody formation continues throughout life, and IgG antibodies do not usually persist beyond the hyperimmunizing stimulus of acute disease. Thus, in *active* brucellosis, 7S (IgG and immunoglobulin A [IgA]) antibodies are produced.[8] The IgG antibodies fix complement better than the IgM and may be detected by the complement fixation test, the indirect fluorescent antibody test or an immunodiffusion study. Blocking antibodies—probably primarily IgA, although this has not been conclusively shown—are also produced during active infection. These nonagglutinating IgA antibodies bind to the surface of the bacteria utilized in the agglutination test and thus prevent IgM antibodies from reacting and forming the cross lattices responsible for agglutination. Therefore, the serum of a patient previously shown to agglutinate brucella may show a prozone particularly at lower titers and actually give a negative reaction following reactivation of the latent infection. If a laboratory were to screen for brucella antibodies at a single low titer, it consequently might obtain a false-negative serologic result. Slide agglutination tests are particularly prone to give false-negative results. Furthermore, all patients do not react with all antigens, even those derived from the same species of pathogen.

To summarize the serodiagnosis of brucellosis (Table 1), prior infection without current active disease is usually attended by the presence of IgM antibody without IgG. If the patient with prior exposure is given a skin test, not only will IgM antibodies be found which may be boosted to a high titer, but the skin test may induce IgG antibodies. If the patient has active disease, IgM antibodies may or may not be shown, due to the prozone phenomenon, but there will be complement-fixing and precipitating IgG antibodies. The same serologic features occur with chronic focal disease, as in our patients. Unfortunately, diagnostic confusion is common in high-risk persons such as veterinarians and farmers who have had remote brucellosis. They are not actively infected but are continually re-exposed and restimulated to develop serological changes resembling those seen in active cases. In such patients, one can only make a conclusive diagnosis by culture.

Brucellae usually require five to seven days to give a positive blood culture. Some strains of B. abortus require carbon dioxide for growth, and if one is considering the diagnosis of brucellosis, it is worthwhile to alert the laboratory to ensure optimal handling of the specimen. The frequently stated difficulty in obtaining positive cultures is not only technical, however. Brucella organisms are not extraordinarily fastidious, and their reputation is largely due to the fact that even in patients with prolonged and recurrent fever bacteria are rarely present in the blood stream, and even then are usually present in very small numbers. Therefore the habit of holding negative blood cultures for long periods of time is unnecessary.

Our first patient demonstrates the serodiagnostic confusion that can arise. The slide agglutination was positive at 1:320 in our laboratory but negative at 1:160; if screening had been done only at some lower titer, the test would be called negative. Tube agglutination results gave somewhat higher titers without prozone formation. However, agglutination tests at the laboratories of the Hooper Foundation and the Department of Microbiology at the University of California,

Berkeley, were negative on this patient's sera. Presumably the antigen used by these laboratories simply did not react at any titer. Complement-fixing antibodies were present in tests at both of these laboratories as expected for active infection.

Immunity to brucellosis is less than completely understood, and is well-reviewed by Elberg,[9] a former pupil of Dr. Meyer. We know that the antibodies which are produced against brucella do facilitate phagocytosis of the organism by macrophages, but the antibodies do not seem to be highly protective. Cellular immunity, mediated by the interaction of immune lymphocytes and macrophages, appears to be the most important determinant of the disposition of this infection, as it is for a host of other infections capable of latency and chronicity, such as tuberculosis and fungal diseases.

Therapy

If patients who become acutely ill are not treated at all, their undulant fever will usually subside within several weeks to a few months, and most patients will not become ill again. Antibiotics provide a prompt defervescence, but unfortunately it is not clear whether the proportion of patients developing chronic disease, probably some 15 percent, is altered significantly.

The usual antimicrobial therapy of brucellosis in adults is 2 grams of tetracycline in divided doses, administered orally for three to six weeks. Because of the tendency to relapse, many physicians select a longer rather than shorter period of treatment. It was once firmly believed that streptomycin should be given in addition to tetracycline, particularly in severe cases. However, the virtues of adding streptomycin have become less clear over the years, and no definitive studies show that the ultimate results are superior to those obtained with tetracycline alone. The inhibitory and bactericidal concentrations of tetracycline for brucella isolates are generally quite low, below 2 micrograms per ml.

In the first case presented today, we administered somewhat radical therapy by initially employing ampicillin. Although ampicillin has been previously reported to be ineffective in clinical brucellosis, one negative study appears to have been in patients without active disease who could not be expected to benefit,[10] while the other includes no data on antibiotic susceptibility of the organisms.[11] We used ampicillin because the literature[12] stated and our *in vitro* laboratory tests showed that the organism was highly sensitive to ampicillin and because the organism was relatively easily killed by ampicillin compared with poorer prospects for killing it by safely attainable levels of tetracycline. The patient had an extremely prompt and gratifying clinical response.

We hoped that bactericidal therapy might make his return for treatment less likely, but pain subsequently developed in the patient's hip. In view of his age and despite the absence of a definable lesion, we reinstituted ampicillin without waiting for a positive cultural diagnosis. Unfortunately, after again improving promptly and receiving six months of additional ampicillin, the patient returned with probable infectious arthritis and osteomyelitis in the head of the femur. Our assumption, although we could not culture the organism out of our patient, was that since new disease developed while the patient was on ampicillin, it might well be a resistant mutant. We therefore chose to change the antibiotic regimen to tetracycline. He has notably improved, and we hope that he will continue to do so. Nonetheless, chronic focal bony disease requires surgical excision if it is to be cured at all. It is unlikely that any course of any antibiotic will prevent this patient from relapsing, particularly if antibiotics are stopped. Our ability to terminate this infectious process depends upon our developing a much greater understanding of the persistence of latent brucella infection and not upon recurrent courses of antibiotics.

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Important Advances in Clinical Medicine

Epitomes of Progress—Ophthalmology

The Scientific Board of the California Medical Association presents the following inventory of items of progress in Ophthalmology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in Ophthalmology which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Ophthalmology of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, California Medical Association, 731 Market St., San Francisco, CA 94103

Ophthalmoscopic Observation of Retinal Nerve Fiber Layer Damage

DISEASES OF THE retina, optic disc, optic nerve and other portions of the anterior visual pathways can be expected to produce direct or retrograde changes in the nerve fiber layer of the retina. Fortunately, this innermost retinal layer is easily accessible to the examining light of the ophthalmoscope. Recent studies have shown the feasibility and clinical value of direct visualization of alterations in the retina nerve fiber layer. Especially when red-free light is used, the details of the nerve fiber layer are readily seen and, with some practice, their alterations in pathological states can be evaluated by everyone who uses an ophthalmoscope. Therefore, careful scrutiny of the nerve fiber layer both in white and red-free light should become an integral part of the normal ophthalmoscopic evaluation of the fundus.

The technique of fundoscopy of the retinal nerve fiber layer involves sharpening one's clinical perceptions to the point where the striated appearance of the nerve fiber layer becomes easily visible. Both white light and red-free ophthalmoscopic evaluation should be used routinely for all patients, and in particular, for those patients in whom there is any question of pathological involvement of the anterior visual pathway. Factors which aid in the observation of the nerve fiber layer are a well dilated pupil, a deeply pigmented choroid and a direct ophthalmoscope with a red-free filter and *bright* source of illumination. Obviously, the media must be quite clear and it helps if a patient is young or otherwise endowed with a thick nerve fiber layer. The fine parallel striations which compose the appearance of the normal nerve fiber layer are most apparent in the immediate peripapillary region, particularly in the arcuate bundles close to the vascular arcades and, especially, along the temporal vascular arcades. These fine striations are most difficult to see in the nasal hemiretina and the much smaller nerve fibers of the papillomacular bundle are easily identified only in the optimum cases.

Patterns of Nerve Fiber Layer Damage. There

may be generalized attrition of the nerve fiber layer, small slit-like defects or sector-shaped defects. Obviously, one or more of these conditions may co-exist. Of course, those diseases which cause only focal destruction of nerve fiber bundles will produce the most obvious defects, because a nerve fiber layer of normal density will provide clear contrast to the area of the defect; focal defects are much more difficult to observe against a background of generalized attrition.

Preliminary studies have already shown the value of this technique in the study of patients with optic nerve disease, glaucoma and ocular hypertension, papilledema, toxic amblyopia and congenital hemianopia.

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Amaurosis Fugax and Its Significance

AMAUROSIS FUGAX is a term signifying transient episodes of monocular blindness. Scattered references extending over a hundred years indicate that at least a few physicians recognized the etiologic implications. Practical appreciation began after 1951 when an article entitled "Transient Monocular Blindness Associated with Hemiplegia" by Fisher in Boston related premonitory blindness as a significant warning of impending stroke. Since many persons experience amaurosis fugax without later development of cerebrovascular accidents, the immediate practical question was how to select those patients who, if untreated, would experience such difficulties.

The typical episodes involve only one eye at a time, last only a few minutes (usually less than five) and, contrary to expectations derived from Fisher's 1951 article, are unassociated with concurrent hemiplegia. In any age group, amaurosis fugax is an indication for obtaining a general health assessment, paying particular attention to possible sources of embolic disease (rheumatic heart disease, subacute bacterial endocarditis), hematologic disorder and vasculitis. Signs and symptoms of neurological dysfunction should be sought. When amaurosis fugax occurs in otherwise healthy young adults (particularly in men), the cause often remains mysterious and episodes are likely to disappear gradually even after occurring for many years.

In middle-aged and older persons, especially those in whom there is a predisposition to significant vascular disease engendered by hypertension, diabetes mellitus or hyperlipidemia, it may be difficult to know with certainty how far to pursue evaluation. Unfortunately, the frequency and severity of amaurosis fugax episodes provide little help, since symptoms may be mild in the presence of surgically correctable, severe disease. Safe and simple tests, such as ophthalmodynamometric determinations of ophthalmic arterial pressure, are prone to false negative results due to collateral circulation. Furthermore, while ophthalmodynamometry may give some indication of significant carotid stenosis, it gives no reliable indication at all of the presence or absence of an ulcerating atherma periodically discharging showers of cholesterol plaques or soft platelet emboli. While a number of investigators are at work attempting to develop sophisticated, noninvasive, electronic tests of carotid and intracranial blood flow, carotid angiography remains the reliable way to study blood flow to the head.

At present, several points may be made about the condition:

- Amaurosis fugax is recognized as an important indicator of possible carotid arterial disease.
- Such carotid disease is frequently extracranial, consisting of stenotic and/or atheromatous ulcerating lesions close to the carotid bifurcation.
- These lesions may be approached with a high degree of safety and success by vascular surgeons performing endarterectomies and grafts.
- In order to find the lesions, carotid angiography is most useful. Despite a considerable risk of complications in the early days, carotid angiography performed by modern techniques is a relatively safe procedure.
- Very safe and sensitive, nonangiographic procedures for estimating abnormalities of carotid blood flow may be applied in the future to detection of primarily stenotic lesions. However, normal values may give a false sense of security when the principal difficulty is embolic rather than stenotic.

• Aspirin may help some patients whose amaurosis fugax is not due to surgically amenable lesions, by lessening platelet aggregation.

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Time Released Medication for Glaucoma

CONTROL OF GLAUCOMA using topical medication has historically been achieved by the use of medications instilled into the conjunctival sac at varying rates of frequency—depending upon the drug used and the requirements of the patient. During the night treatment is usually reduced and, therefore, control during these hours is less certain. Various drugs and vehicles have been used to reduce to a minimum the number of instillations required in 24 hours. Physostigmine, demecarium bromide, echothiophate, pilocarpine and other antiglaucoma medications have been combined with ointment bases or in vehicles containing polyvinyl alcohol, methylcellulose or Absorbobase.® Contact is claimed to be prolonged and therefore the agents are effective for a longer period of time. It is likely that toxic levels of the drug occur with each instillation while therapeutic levels are achieved only part of the time with pulse therapy.

As a natural evolution, new systems of delivery have been investigated. Among these are administration by saturated hydrophilic contact lenses; through a copolymeric membrane permitting passage of drugs at a predetermined rate; through devices that hydrolyzed, releasing medication and degrading to self-destruction, or by the use of capsules with two compartments—one absorbing water by osmosis then, by expansion into the second chamber, forcing medication out through an opening calculated to deliver a therapeutic dose.

To date the only system available is the Pilocarpine Ocusert.® This wafer-shaped device consists of a core of pilocarpine and alginic acid surrounded by a copolymeric membrane. In a watery atmosphere (tears) the drug passes out of the core at a preset rate. Alterations in the nature of the copolymeric membrane can be made to control the release rate. Two Ocuserts® are now available: Pilo-20 and Pilo-40. The Pilo-20 Ocusert® releases pilocarpine at 20 micrograms (μg) per hour and the Pilo-40 at 40 μg per hour. Therefore, the amounts of drugs required with this delivery system are some 10 to 25 times less than with pilocarpine drops. There is also the theoretical advantage that the drug is being delivered day and night.

JOSEPH G. TIRICO, MD

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Studies of the Optic Nerve Head in Glaucoma

RECENT ADVANCES in clinical evaluation of the optic disc place emphasis on the three dimensional morphology of the optic cup and the differentiation of the amount of pallor from the extent of cupping.

Studies on the qualitative appearance of the cup in the early stages of glaucoma have described the processes of central deep atrophy and upward-downward extension. The former occurs in discs with congenitally small cups which, before the onset of atrophy, did not extend to the lamina and is manifested by a "moth-eaten" appearance of the prelaminar nerve head tissue with apparent deepening of the cup in that central area. Upward or downward extension can be detected by the presence of vertical ovality of the cup which is measured by a greater vertical than horizontal cup to disc ratio. Thorough evaluation of the nerve head is increasingly dependent on the use of the slit lamp with which a stereo view can be obtained.

Using this instrument it is also possible to distinguish between the size of the optic cup and the degree of pallor. Unfortunately, use of the monocular direct ophthalmoscope to observe the disc may easily disguise the difference between these two parameters since it does not provide a good three dimensional view. Because the area of pallor

is frequently smaller than the area of cupping, increasing disc atrophy can be overlooked when pallor alone is used as a diagnostic guide.

The question of how best to record these observations has also become an important one. Where a fundus camera is available, a stereo photograph is a useful recording medium. Where it is not accessible, the use of geometric terms such as funnel, cylinder or hemisphere in addition to horizontal and vertical cut-to-disc ratios will suffice. Notation of the location of cup pallor will complete the picture and form a composite which can be of continuing value in following any patient.

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Temporary Press-On Visual Aids

PRISMS HAVE BEEN USED for many years in treating strabismus but have not previously received wide patient acceptance when of significant strength because of their heavy weight and cosmetically unacceptable appearance in spectacles. Lightweight plastic membranes which adhere to the back surface of spectacle lenses have recently been developed (Figure 1). These use the Fresnel principle by having a series of long narrow adjacent prisms molded into them, effectively creating high prism powers in a thin lightweight membrane. The availability of these devices has dramatically increased the usefulness of prisms and has reawakened interest in prism therapy by ophthalmologists and orthoptists. Morover, prisms may be varied in power and orientation before the eye without necessitating grinding new spectacle lenses, thus avoiding significant expense to patients. Also available are press-on spherical lenses which may be used for temporary modifications of refractive corrections, again without requiring a new pair of spectacles for a patient. The major disadvantage of the press-on aids is a slight decrease in clarity of vision through them, compared with optically surfaced glass. An additional problem is the possible tendency of practitioners to select this convenient form of therapy rather than a more involved approach which may, however, be more effective in treating a specific case.

ALAN M. ROTH, MD

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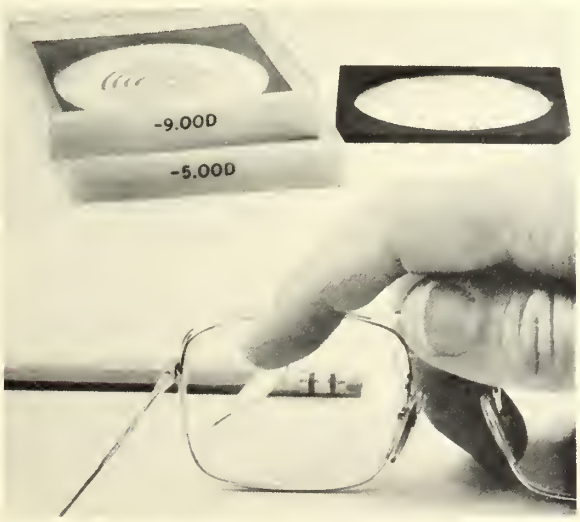

Figure 1.—Newly developed press-on membrane adds prism to spectacle lens without appreciably increasing thickness or weight.

Ophthalmic Microsurgery

THE OPERATING MICROSCOPE is coming of age in ophthalmic operations. For years skilled eye surgeons have done microscopic surgical procedures on a delicate organ which must be treated with extreme precision and care because of its optical as well as its physiological characteristics. In a real sense this type of operation has been a matter of feel and experience because of the relative inadequacy of magnification available in operating loupes. New instrumentation and new training facilities now make it possible to control surgical maneuvers using high magnification and direct visualization which force even the novice to handle tissues with the delicacy and respect of a virtuoso surgeon.

A major impetus in the popularization of ophthalmic microsurgery has been the development of

microsurgical sutures. Fine exquisitely sharp needles fused onto 10-0 nylon suture material have advanced the state of corneal repair measurably in recent years. Never before has so fine a suture been as strong and produced so little corneal reaction. Precise anatomic repair with minimal effect on the optical properties of the tissue is a goal which is within the modern ophthalmic surgeon's grasp because of the availability of these sutures. His facility in using fine sutures has improved greatly largely as a function of his ability to use the operating microscope.

Refined suture materials are not the only reason for using the operating microscope, and more and more surgical procedures are being developed which are done better because of the microscope. These include such microsurgical procedures for glaucoma as trabeculectomy and trabeculotomy, newer cataract procedures such as phacoemulsification and phacofragmentation, cataract aspiration procedures, pupillary membrane discissions, anterior chamber reconstruction, intraocular tumor resection, corneal laceration repair, corneal transplantation and a variety of surgical procedures involving the vitreous.

In addition to those operations clearly improved by the use of the microscope, more and more surgeons are using this instrument for all ophthalmic surgical procedures—including cataract extraction. Although many ophthalmologists do cataract extraction without the microscope, others now find that the microscope adds a degree of visual control which is otherwise unavailable. If a complication should occur during an operation, such as a lens capsule rupture, an intraocular hemorrhage or a vitreous loss, the surgeon who already has the microscope trained on the surgical field is far better prepared to deal with the problem than the man who must then obtain and adjust the scope or do without it entirely.

The future direction of ophthalmic operations is definitely toward increasingly sophisticated magnification systems which allow control of delicate procedures which was heretofore unavailable. Many procedures are now done which could not have been done without the operating microscope, many standard procedures are now done better with it and many new procedures will undoubtedly be developed because of it.

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Current Concepts in the Diagnosis and Treatment of Retinoblastoma

WHILE RETINOBLASTOMA remains the most common intraocular neoplasm in children, it is seen infrequently by both ophthalmologists and pediatricians. However, prompt recognition of a child with possible retinoblastoma may frequently result in saving both life and vision. The most common presenting signs of retinoblastoma are leukokoria (white pupil) and strabismus. Young children with either of these two findings must have a complete retinal examination by an ophthalmologist. Usually, ophthalmoscope appearance substantiates the diagnosis. Occasionally, unusual presentations and bizarre retinal findings contribute to difficulty in arriving at the correct diagnosis. In these puzzling cases, anterior chamber paracentesis may show elevated lactic dehydrogenase (LDH) activity when compared with the serum level of this enzyme. LDH levels have not been elevated in cases of leukokoria caused by diseases other than retinoblastoma. Very recently, a report has indicated successful development of a specific skin test for retinoblastoma using crude membrane extracts of retinoblastoma cells developed in tissue culture. Substantiation of the elevated aqueous LDH levels and skin test specificity is required, but both appear to be promising diagnostic aids. Anterior chamber paracenteses for tumor cells, P-32 uptake studies and B-scan ultrasonography may be helpful diagnostic additions in specific cases.

Prompt diagnosis and aggressive treatment have resulted in very encouraging survival rates in this potentially lethal disease. Enucleation and radiation remain the principal therapeutic choices. Currently, the therapeutic trend is gradually swinging toward the increased use of radiation. This is due to the improved results from utilization of both the linear acceleration and high doses of irradiation. A recent report suggests an overall survival rate approaching 90 percent for retinoblastoma. In the past, chemotherapy had been used primarily to augment radiation therapy in trying to eradicate the specific ocular tumor. Tricthylenemelamine (TEM) administered by carotid artery injection was the principal drug used for this purpose in the United States. Because of the increased success of radiation therapy, this is now needed only in very isolated cases. Instead, chemotherapeutic emphasis is now directed toward prophylaxis in patients who are at high risk for

metastatic disease. Systemic drugs are administered weekly for two years. The decision of which cases require such treatment is, at present, the subject of debate among physicians currently caring for these children.

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Electroretinography and Retinal Function Testing

WITH RECENT IMPROVEMENTS in instrumentation and technique, special tests of retinal function have become increasingly valuable in the total assessment of retinal disorders.

The electroretinogram (ERG), long studied with regard to wave form analysis, is now better understood in terms of the cellular origin of the various wave components. The time dependent relationships of the ERG are recognized as being more stable than alterations in amplitude, and an appreciation of the value of threshold determination (long recognized by basic science workers) is growing among clinical investigators.

Recent studies of various forms of hereditary retinal pigmentary degeneration (that is, retinitis pigmentosa) have shown the value of electroretinography as a means of identifying minimally affected persons and those representing the carrier state. Together with visual fields and dark adaptation measurements, changes in the ERG help the clinician to monitor the course of these and other progressive disorders.

Dark adaptometry is still a valuable adjunct to electroretinography for separating rod from cone disorders. This is true despite the knowledge that there are many areas of functional overlap in which rods and cones seem to share physiologic features originally thought to be mutually exclusive.

An electro-oculogram (EOG)—an electroencephalographic tracing made by moving the eyes a constant distance between two fixation points—in certain instances can provide information not readily obtainable from the ERG. The EOG appears to be more sensitive to focal macular changes than the ERG, and this can be very helpful. It is technically easier to obtain than the focal ERG, which requires very complex instrumentation and a high degree of patient cooperation.

Interest in the visually evoked potential (VEP) is increasing. The test is relatively easy to do, but requires computer enhancement and averaging. A major disadvantage of this test is the difficulty of interpreting the results, because the individual portions of the complex wave are incompletely understood. Still, the VEP can provide information about macular function, as reflected by the occipital electroencephalographic response. This is especially useful in pediatric cases where other tests of visual function are impossible to obtain.

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Phacoemulsification

PHACOEMULSIFICATION is a method of emulsifying and aspirating a cataract with the use of a hollow needle vibrating at 40,000 cycles per second. The surgical instrument system includes irrigation and aspiration components, and allows for partial removal of a cataract through a small surgical incision (2.5 to 3 mm). In addition to a small surgical wound, phacoemulsification allows for the preservation of a round pupil. There are fewer postoperative problems of corneal astigmatism and corneal hypesthesia with its use. Fewer problems with wound closure are encountered, and the incidence of hyphema and flat anterior chamber is less.

The technique is ideal for congenital cataracts and for soft cataracts in young patients where intracapsular extraction would be most difficult. It is contraindicated in corneal dystrophy, uncontrolled glaucoma, and shallow anterior chamber, and in patients with poor pupillary dilation. Phacoemulsification is a demanding technique. Surgeons performing it must be properly trained, have stereopsis, and be thoroughly familiar with the use of the operation microscope. This tech-

nique allows for extracapsular cataract removal, in which not all of the lens is removed. All or part of the posterior lens capsule is left in place, which allows for later re-formation of secondary cataracts. For this reason, an opening in the posterior capsule (capsulotomy) is frequently made at the time of the operation. Irritation of the iris by the high frequency vibration leads to some degree of iris atrophy in most cases. There is more postoperative anterior uveitis, as would be expected with extracapsular lens removal. This is usually modified by subconjunctival steroid therapy.

One of the more common complications after phacoemulsification is corneal edema, which is usually transient but may be long-lived. This requires therapy with dehydrating agents and steroids. Compared to intracapsular cataract extraction, the procedure may theoretically lessen the incidence of macular edema and/or retinal detachment, and limit the amount of vitreous in the anterior chamber. However, the equatorial and subcapsular lens remains which persist after phacoemulsification, impair visualization of the retina, particularly in the periphery. This may complicate the repair of retinal detachments when present.

Phacoemulsification is a valuable surgical technique, which offers a new dimension in cataract surgery. It should be selectively used, and evaluated by unbiased observers.

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EDITORIAL

In Defense of Health Care

IT MAY HAVE BEEN NOTED that the writer of many of the editorials appearing in these columns has used the terms medical care and health care more or less interchangeably. This has been disturbing to some who believe that physicians have responsibility for medical care but cannot be held responsible for health care. Spokesmen for one large medical association have gone so far as to define medical care as that portion under the control of the physician, and health care to include social, economic and environmental influences beyond the control of medicine. But this distinction is hard to maintain, particularly when there is considerable evidence that the role of the physician is substantially diminishing in much that is medical care and is substantially increasing in much that is called health care.

The distinction is further blurred by the increasing use of the word health in medicine and medical care and by the increasing number of meanings and connotations which are being given to this word. The terms health insurance, health benefits, health centers, health sciences, health maintenance and health screening all clearly pertain to medical care. And in another dimension health and even medical care are being linked to the concepts of well-being and even the quality of life, concepts which have not traditionally been considered part of medicine and do not necessarily depend upon the absence of disease or infirmity. But linked they are becoming, and one can even sense a return to the all embracing root meaning of the word health in which the words heal and whole come together as one.

In any case physicians really no longer have true control of medical care, if indeed they ever did. And it is equally true that physicians no longer can remain aloof or apart from the social, economic and environmental influences on health and well-being, if indeed they ever could. When one gets right down to it, health is what medicine is all about, whether one is talking about coping with illness or injury; adjusting to stresses in the internal or external environments; striving to achieve, restore or maintain physical and mental well-being (as health is defined by the American Medical Association), or physical, mental and social well-being (as it is defined by the World Health Organization).

For these and many other reasons the distinction between medical care and health care seems no longer to be very important, and if anything—to this writer at least—health care seems to be the more inclusive and therefore the more useful term.

—MSMW

The Diagnosis of Obstructive Jaundice

THE DIFFERENTIATION between surgically correctable and noncorrectable causes of cholestatic jaundice remains a diagnostic challenge.

In the past decade, the multiplicity of the conditions not amenable to surgical operation—largely drug-related hepatitis—has greatly increased, and now constitutes a large share of such conditions. In general, for that portion, there is usually no effective treatment as yet, other than removal of an offending drug or toxin and general support.

But the *early* recognition of the surgically remediable conditions remains highly important to permit their correction before the hepatic status has deteriorated, a localized tumor has spread or bacterial cholangitis has developed or extended.

Each physician must develop his own strategy of diagnostic approach to these conditions. His

choice of diagnostic methods and sequences will vary with his experience, the availability of specific procedures to him and, especially, the personal skills and record of accuracy and morbidity of persons offering these. As new procedures and opportunities appear, one's strategy must adapt.

In this issue of the JOURNAL a group of interdepartmental authorities at the University of Oregon Hospital present their current formula for approaching these conditions. They have been leaders in developing and demonstrating the application of the three major diagnostic procedures described. Applying these with great personal skill, their scheme of approach to sorting out cholestatic jaundice is logical and their results impressive. Groups of physicians elsewhere, with the availability of a different array of procedures and skills, would need to select somewhat different methods and sequences; however, the same general sorting schemes should hold.

Endoscopic retrograde cannulation of the biliary ducts (ERCB) is dramatically and rapidly replacing percutaneous transhepatic cholangiography for delineating the gross anatomy of the main biliary tree. It offers an immediate and decisive identification of gross bile duct obstructions, usually with much less morbidity than occurs with transhepatic cholangiography. ERCB requires great personal skill, and will never be within the standard armamentarium of the "routine" good fiberendoscopist. In skilled and experienced hands, it is successful in at least 85 percent of patient tries. In medical centers where ERCB is not yet adequately available, percutaneous transhepatic cholangiography may still be pursued with reasonable success. The technique for this procedure has undergone improved modifications recently, such as those described by a Japanese group.[1] Its accuracy and morbidity varies widely from center to center, and it is certainly highly unpopular and even dangerous in many.

The Department of Radiology at the University of Oregon is one of relatively few in this country highly capable in doing transjugular cholangiography (TJC). ERCB, as a less invasive procedure, is far more attractive. However, as a back up for solving ERCB procedure failures, TJC has attraction in those institutions possessing the skill, and is probably less risky than a percutaneous approach.

Many readers will be surprised to read the statement that selective visceral angiography "is of great value in the differential diagnosis of obstructive jaundice." This is probably entirely true in Josef Rösch's meticulous master's hands, but not so for the ordinary angiographer. In the latter setting, angiography should be viewed as a valuable accessory technique to search for anticipated hepatic metastases, to define limits of expanding tumors and to outline the position of major vessels preoperatively in order to plan more accurate surgical approaches. Dr. Rösch emphasizes the wisdom of doing angiography before transjugular cholangiography, in order to increase the safety of TJC.

After the easier patient material has been sorted and identified, needle liver biopsy by any route is usually very disappointing for differentiating the remainder. The tiny fragments obtained by the transjugular approach from areas adjacent to major vascular trunks would usually be considered inadequate and nonrepresentative of the main hepatic parenchyma—a very poor substitute for the 1.5 to 2 cm long cylinders usually obtained by the standard percutaneous method.

The authors have wisely relegated nuclear scanning to a minor place in this particular problem. Its definition of hepatic metastases is not often found in livers that are of relatively normal size, and rose bengal scans, in general, have a rather poor record for differentiating extrahepatic biliary obstruction from intrahepatic cholestasis.

"Minilap," developed by Dr. David State and his associates,[2] and similarly reported by Wexler et al,[3] is undoubtedly a very reasonable—though more invasive—immediate and definitive approach in selected cases, to be employed by skilled interdepartmental teams. Similarly, peritoneoscopic combined needle liver biopsy, transhepatic cholangiography and selective transhepatic portal venography is found useful in certain centers in western Europe.

In many hospitals in this country, early exploratory full laparotomy is still practiced for this diagnostic problem. Though the outcome may be satisfactory for roughly half such cases, the failure to obtain additional preoperative information through the types of procedures herein described often increases operative morbidity, necessitates a further full laparotomy and in some instances is simply disastrous.

Even in the future, some of the more definitive diagnostic procedures for these conditions which require great skill will be available only in large medical centers. A primary care physician should

be alert to refer selected patients sufficiently early in the course of their puzzling cholestatic jaundice to those locations where appropriate measures can be applied for the best advantage of the patient.

As the number of available procedures in the larger medical centers increases, physicians in these centers are also required to make wise decisions about how much of the potential comprehensive information is truly needed—in relation to expense and morbidity—in order to solve expeditiously each jaundiced patient's diagnosis and define treatment. In this connection, I applaud the diagnostic approach of the Oregonians, who choose early the least invasive, usually decisive procedures, which are relatively few in total number.

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Probabilities and Patient Care

EVERY PRACTICING PHYSICIAN lives with the reality of probabilities in patient care. Almost every one of his acts or decisions is the result of his assessing the probabilities of benefit to the patient as against the probabilities of complications or an untoward outcome. In each instance he is aware of the statistical possibilities of unwanted complications or undesired outcome and in each instance he takes this into account. Sometimes the probabilities involved are known rather precisely and sometimes they are not. Often the urgency is such that decisions must be made and action taken using incomplete information. Always there is a risk involved, for both physician and patient, when any decision is made or any action taken in patient care. Sometimes the risk is large as when an experimental treatment is undertaken for an as yet incurable disease, and sometimes it is almost infinitesimal as when prescribing an aspirin tablet for a patient not known to be sensitive to aspirin. But the risk and the possibility of an undesired result based on the probabilities inherent in the situation are always present.

When such an undesired result occurs, the patient or the patient's family, or an attorney who may be involved, may see this as an injustice to the patient or due to some mistake by the physician, and therefore seek compensation or damages through the courts. The question of any malicious intent on the part of the physician is almost never at issue. Rather the presumption is that since things did not turn out right something must have gone wrong somewhere and therefore someone or something should be held to account. In instances where actual malpractice has occurred this is valid enough. But when the practice was correct yet the result was an unwanted one, it is quite likely that the particular case fell within the lesser but nevertheless very real statistical probability of an undesirable outcome.

Natural science recognizes probabilities such as these and so does mathematics, which is the language of the natural sciences. Unfortunately the laws which men make to govern themselves are generally based on a different premise and tend not to reflect these probabilities which are so fundamental to natural and biological law—and to patient care. In consequence, the public view seems to be that when a patient is so unfortunate as to find himself among that portion or percentage whom the natural probabilities predict will have an unfortunate or less than perfect result, that patient is thought somehow to have been wronged. This view is now so widely held and has reached such proportions that the mechanisms of providing compensation to patients for this kind of misfortune are proving unequal to the task and a major crisis in patient care is rapidly developing.

An article appearing in this issue addresses the very basic problem of finding some way to bring a scientific assessment of probabilities in patient care to bear in the law as it affects medical practice. It could be an important pioneering contribution to the vexing and so far unsolved "malpractice" problem which now plagues both medicine and the society it is trying to serve.

—MSMW

Systolic Click and Late Systolic Murmur

INFORMATION ON SYSTOLIC CLICKS and late systolic murmurs was at a virtual standstill for half a century after Gallavardin's description in 1913 when he related systolic clicks to pericardial adhesions found at necropsy. Since systolic clicks often (but not invariably) introduce late systolic murmurs, and since the physiologic mechanisms of systolic murmurs proposed in the mid to late 50's did not explain murmurs confined to late systole, both of these auscultatory events continued to be regarded as "extracardiac."[1] The systolic whoop or honk, described by Osler in 1880, was not even remotely considered in the same context.[2] In the early 1960's, isolated late systolic murmurs as well as clicks with late systolic murmurs were attributed to mitral regurgitation. This was a major step forward.[1] New data then began to accumulate, at first slowly, then in the last few years, logarithmically. We are now faced with an information explosion over what for nearly 50 years lay dormant as an innocent auscultatory curiosity. It is therefore timely for THE WESTERN JOURNAL OF MEDICINE to publish a specialty conference on this topic.

The 1960's introduced what might be called the "leaflet-chordal" phase of our knowledge of clicks and late systolic murmurs. Left ventricular angiocardiography convincingly showed systolic prolapse of the posterior mitral leaflet together with mitral regurgitation.[1] Response of the late systolic murmur to vasoactive drugs (amyl nitrate and pressor agents) was sufficiently similar to the response of the holosystolic murmur of mitral regurgitation to lend weight to the angiocardiographic conclusions. The technical capability of recording sound from within the heart, especially the left heart, permitted localization of both the clicks and late systolic murmurs to the left atrium, a site appropriate for origin due to an incompetent mitral valve.[3] Left ventricular cineangiography recorded simultaneously with cine-trace phonocardiograms allowed precise timing of clicks and late systolic murmurs, and clearly showed that mitral regurgitation started in late systole. Prolapse of the mitral valve was ascribed to leaflet-chordal redundancy which permitted early systolic competence but caused late systolic overshoot. The clicks were ascribed to abrupt tensing of the elongated chordae and redundant leaflet tissue (chordal snaps). Other mechanisms were not entertained at that time.

A general interest in auscultatory responses to *physical* maneuvers became popular as clinicians sought more practical alternatives to the administration of amyl nitrite or pressor agents. Valsalva's maneuver, squatting, prompt standing and isometric exercise (hand grip) were applied with advantage to patients with isolated clicks and clicks with late systolic murmurs. The response not only increased the diagnostic yield in such patients, but in some served to provoke systolic whoops or honks, indicating that the auscultatory spectrum included clicks, late systolic murmurs as well as the high pitched musical whoop.

Careful phonocardiographic study of the response to physical and pharmacologic interventions showed that the click and late systolic murmur migrated toward or away from the first heart sound as left ventricular volume decreased or increased. Accordingly, the mid to late systolic click could be made to appear in early systole and the late systolic murmur seriatim became holosystolic or nearly so. It was then shown that spontaneous occurrence of early systolic clicks occasionally introduced long systolic murmurs. It became necessary to distinguish systolic clicks of mitral origin from ejection sounds of semilunar valve or great vessel origin.

The next stage in our knowledge can be designated the "myocardial phase." Apex or kinetocardiograms in patients with clicks and late systolic murmurs sometimes recorded bifid left ventricular impulses;[2] shortly thereafter, left ventricular cineangiograms established the presence of contraction abnormalities of the left ventricle. Initial observations on inferior wall abnormalities were extended to include posteromedial contraction with anterior convexity, ring-like contraction of the mid portion of the left ventricle, inadequate long axis shortening, posterior akinesis and cavity obliteration similar to that seen in hypertrophic obstructive cardiomyopathy (idiopathic hypertrophic subaortic stenosis).[4] The degree of contraction abnormality ranges from hypokinesis to frank dyskinesis, and has prompted some investigators to designate the click-late systolic murmur

complex as a segmental cardiomyopathy that throws the chordae and leaflets into a slack position allowing late systolic prolapse of the mitral valve.[5] However, it is difficult to know which comes first; do redundant chordae and leaflets result in segmental abnormalities of left ventricular contraction or vice versa?

Up to this point, a left ventricular angiocardiogram was the final arbiter in providing precise diagnostic information. Phonocardiograms and apex or kinetocardiograms were useful but indirect noninvasive tools. *Echocardiography* was ideally suited for the direct study of the click-late systolic murmur complex since it provided safe, painless, noninvasive information; could be repeated easily and frequently, and could define precisely movements of the mitral leaflets. It is no wonder that the number of diagnosed cases has risen precipitously because of liberal use of echocardiograms and investigation has flourished.[6] Mitral leaflet motion can now be defined in previously ambiguous instances of isolated systolic clicks without late systolic murmurs, and echocardiographic recordings can be made after provocative tests such as amyl nitrite inhalation. Relatives of propositi can be studied, shedding light on familial incidence. In addition, echocardiography has provided further anatomic information. Since the ultrasound beam is most precise and reproducible in recording anterior mitral leaflet motion, it is not surprising that a relatively high incidence of *anterior* as well as posterior leaflet prolapse was found. More recently, left ventricular angiocardiography has confirmed frequent prolapse of either or both mitral leaflets and, in addition, right ventricular angiography has disclosed asynergy of that chamber as well as tricuspid leaflet prolapse.[4] During the course of such studies, coronary cineangiography has generally shown normal vessels, but more recently, coronary arterial abnormalities have been described, including corkscrew appearance of major vessels or their branches, short main left coronary artery and anomalous origin of the right coronary artery.[4] The significance of these observations is not yet clear.

The clinical aspects of the click-late systolic murmur complex have expanded in parallel with the anatomic and physiologic information cited here. At one end of the spectrum are persons with neither clicks nor late systolic murmurs but with echocardiographic evidence of mitral leaflet prolapse. Starting at this point, the clinical scope broadens considerably to include a variety of features in the physical signs, chest x-ray studies, history and electrocardiograms, as well as a number of significant complications and associations with other cardiac diseases.[2]

The auscultatory hallmarks—mid to late systolic clicks and late systolic murmurs—may be absent, intermittent, present individually or in combination, variably accompanied by systolic whoops or honks and influenced by a variety of physical or pharmacologic interventions. Palpation of the left ventricular impulse may be normal or may detect a double (bifid) systolic impulse recalling but not necessarily paralleling the abnormal contraction patterns seen on left ventricular angiocardiography. Physical appearance and x-ray films of the chest show relatively frequent thoracic bony abnormalities, especially loss of thoracic kyphosis (straight back), decreased anteroposterior chest diameter, scoliosis and pectus excavatum. It is not yet clear whether these abnormalities are independent of or formes frustes of Marfan's syndrome in which unusually long chordae tendineae, laxity of mitral valve tissue and clicks and late systolic murmurs have been found.[7]

The electrocardiographic abnormalities initially emphasized were T wave inversions in inferior leads, but the range has considerably increased. Rhythm disturbances vary from occasional atrial or ventricular premature beats to supraventricular tachycardia, atrial fibrillation and ventricular tachycardia. Arrhythmias may occur at rest, but exercise testing has been used to provoke occult arrhythmias or to determine the extent to which physical exertion aggravates them. Sudden death (mentioned later) has been attributed to arrhythmias. Inverted T waves are not confined to inferior leads but appear in lateral precordial leads and are occasionally accompanied by ST segment abnormalities. QT prolongation has been reported, but no relationship has been established between QT prolongation, ventricular arrhythmias, deafness and sudden death in these patients. In addition, sinus bradycardia, and first, second or complete heart block has been mentioned.

The history is important in several respects. Female prevalence of the click-late systolic murmur syndrome approaches 80 percent. Familial occurrence is well established and now easy to document because of echocardiography. Mild fatigue and dyspnea are often present without acceptable physiologic explanation. A high inci-

dence of psychological disorders has been described, but the prevalence and significance of such disorders are unknown. Despite the frequency of arrhythmias, syncope or presyncopal symptoms are exceptional. In addition, chest pain is a relatively common complaint. The pain is almost always atypical in quality, location, duration and relation to exercise; the pain only rarely resembles angina, is generally mild but occasionally incapacitating, occurs with angiographically normal coronary arteries and is unassociated with chest wall tenderness. The authors of the Specialty Conference call attention to their own work which has shown that the atypical chest pain can be reproduced by elevating systemic arterial and left ventricular systolic pressures with intravenously administered phenylephrine.[8] If the pain originates from regional discrepancies between oxygen supply and demand (papillary muscles, contraction abnormalities), then an increase in left ventricular wall tension with phenylephrine could provoke or aggravate this discrepancy. It may be noteworthy in this regard that propranolol therapy has met with some measure of success in relieving the chest pain although these results are inconclusive.

There are three important complications of the click-late systolic murmur syndrome. Sudden death is the most dramatic and widely heralded.[9] The cause has not been established but a relationship among sudden death and arrhythmias, abnormalities of left ventricular wall motion and familial occurrence is commented upon in the Specialty Conference. The incidence of sudden death is unknown, but all evidence indicates that prevalence is very low. The second important complication of the click-late systolic murmur syndrome is infective endocarditis. This comes as no surprise in view of the known susceptibility of incompetent mitral valves to infection. It has also been shown that infective endocarditis can develop in patients with isolated clicks, *no* late systolic murmur and presumably no mitral regurgitation, although the degree of susceptibility in this context has not been established. The third complication is rupture of chordae tendineae which can understandably follow infective endocarditis, but interestingly, may occur spontaneously.

The systolic click-late systolic murmur occurs not only in the setting discussed above, but occasionally in association with other cardiac diseases. Comment has already been made on clicks, late systolic murmurs and mitral regurgitation in Marfan's syndrome.[7] Mitral valve prolapse has also been documented in otherwise uncomplicated ostium secundum atrial septal defect.[10] Such patients may or may not have clicks and late systolic murmurs. Because of this association, it is desirable that all patients with secundum atrial septal defects have mitral valve echocardiograms. Clicks, late systolic murmurs and mitral valve prolapse have been described in coronary artery disease and related to systolic prolapse caused by papillary muscle dysfunction.[11] In idiopathic hypertrophic subaortic stenosis (hypertrophic obstructive cardiomyopathy) there is characteristic systolic anterior movement of the anterior mitral leaflet after initial closure. Late systolic mitral regurgitation is common and has been held accountable for the occasional resemblance of the systolic murmur to mitral leaflet prolapse. In addition, midsystolic clicks have been observed in idiopathic hypertrophic subaortic stenosis, but the incidence must be very low and the mechanism is unclear.

We do not yet know whether the systolic click and late systolic murmur information explosion has passed its peak. However, it is likely that lively interest in this topic will continue for some time.

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CASE REPORTS

Refer to: LeClerc M, Giammona ST: Coccidioidal meningitis—The use of amphotericin B intravenously and intrathecally by repeated lumbar punctures. West J Med 122:251-254, Mar 1975

Coccidioidal Meningitis

The Use of Amphotericin B Intravenously and Intrathecally by Repeated Lumbar Punctures

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COCCIDIOIDAL MENINGITIS in children continues to be a major cause of granulomatous meningitis and was uniformly fatal before the advent of amphotericin B therapy. The use of amphotericin B has presented many problems related to dosage, duration of therapy and toxicity of the drug—chiefly on the kidney. Winn has reported that cisternal injection is the best method in treating adults with coccidioidal meningitis.[1]

This report describes the clinical and laboratory findings and response to therapy in a child with coccidioidal meningitis treated with amphotericin B administered intravenously and intrathecally by lumbar puncture. Cisternal injections were not given.

Report of a Case

A 2¾-year-old white boy was admitted to Children's Hospital of San Francisco in 1971 for the evaluation of fever, cough, vomiting and increasing lethargy. The patient was in reportedly good health until six weeks before admission, when the mother consulted a physician because the child had fever and was coughing and vomiting. An infection was suspected and treatment was begun using acetysalicylic acid and then penicillin and sulfisoxazole (Gantrisin®). However, intermittent fever with temperatures up to 101°F (38.3°C), and decreased activity continued and the patient was admitted to the local hospital.

On physical examination at admission, the patient was seen to be well nourished, alert and active. There were no abnormal findings except fever elevation. A workup for acute infection was carried out, including a lumbar puncture. There were no abnormalities discovered except for the cerebrospinal fluid (CSF) which contained 204 leukocytes, with 74 percent neutrophiles and 26 percent lymphocytes. Cerebrospinal fluid protein was 60 and glucose was 20 mg per 100 ml. Partially treated bacterial meningitis was suspected and treatment was begun with ampicillin and, subsequently, chloramphenicol. Blood and CSF cultures subsequently showed no growth. Response to a skin test for tuberculosis was negative, and a skin test for coccidioidomycosis showed 1 cm of erythema at 48 hours, but no induration. The child continued febrile and very irritable in spite of therapy and was then transferred to Children's Hospital of San Francisco.

Review of the medical history showed that the child resulted from the mother's first pregnancy, which was full term and normal. He was born at the local hospital in Visalia, California in the San Joaquin Valley. Birth weight was 8 pounds, 13 ounces, and no neonatal problems were encountered. The developmental milestones were passed normally with the child walking at eleven months and talking at 12 months. There was no history of serious illness, convulsive disease, high fevers, pneumonia or allergies to food or medication. The patient had never before been admitted to hospital and had lived only in California. The family history was unremarkable; the mother and father were living and well and a 9-month-old sister was in good health.

On physical examination at admission, the patient was found to be very irritable, with a tem-

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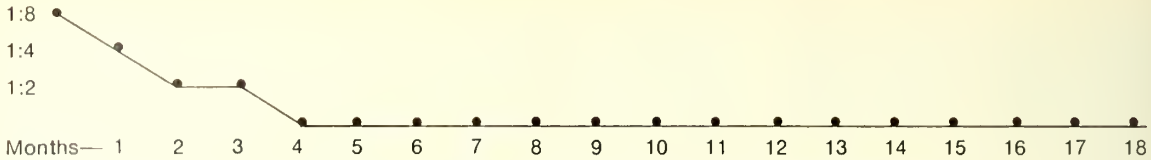

Chart 1.—Cerebrospinal fluid complement fixation titers for coccidioides immitis. (Studies done by Demosthenes Pappagianis, MD, PhD, University of California, Davis, School of Medicine)

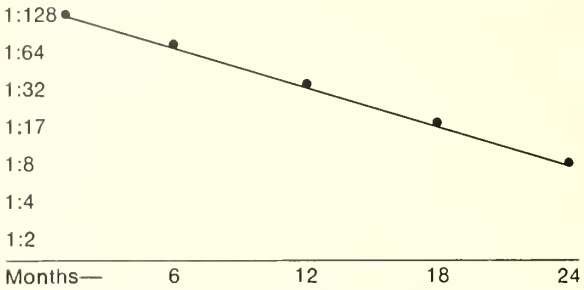

Chart 2.—Serum complement fixation titers for coccidioides immitis. (Studies done by Demosthenes Pappagianis, MD, PhD, University of California, Davis, School of Medicine)

perature of 103°F (39.4°C). Apparent frontal cranial enlargement along with minimal gait ataxia was noted but the remainder of the physical examination, which included a detailed neurological examination, was unremarkable.

Laboratory analysis showed a hemoglobin count of 10.9 grams per 100 ml, leukocytes 16,300 per cu mm, with 64 percent neutrophiles, 28 percent lymphocytes and 6 percent monocytes. Results of urinalysis were normal. Lumbar puncture done on admission showed an opening pressure of 380 mm of water with good dynamics and a closing pressure of 320 mm. The fluid was clear. Examination of the CSF showed 91 cells, 74 percent lymphocytes and 26 percent neutrophiles. The CSF protein was 33 and the CSF glucose was 12 mg per 100 ml (blood glucose 87 mg per 100 ml). Gram stain, India ink preparation and acid fast smear showed no organisms. The total lactic acid dehydrogenase in the CSF was 8 units (normal 5 to 25 units). Roentgenograms of the skull showed spreading of sutures. Bilateral carotid and vertebral cerebral arteriography were carried out and showed diffuse swelling of the brain, with a localized swelling posteriorly in the left temporal lobe. There was evidence of perivascular disease constricting the arteries and veins over the surface of the brain. No abnormalities were noted on brain scan.

Coccidioides immitis complement fixation titers were positive in both the serum and cerebral spinal fluid (Charts 1 and 2). Precipitins for coccidioidomycosis were negative and remained negative. Response to a skin test for coccidioidomycosis was negative at 48 hours.

Laboratory studies showed serum electrolytes of sodium 140 milliequivalents (mEq), potassium 4.0 mEq, chloride 105 mEq, carbonic acid 20 mEq, blood urea nitrogen 6 mg per 100 ml and creatinine 0.5 mg per 100 ml. The febrile agglutinins were negative. Immunoglobulins showed immunoglobulin A (IgA) 230 mg per 100 ml (normal range 39 to 113), immunoglobulin G (IgG) 1,000 mg per 100 ml (normal range 556 to 1,272), and immunoglobulin M (IgM) 140 mg per 100 ml (normal range 55 to 139). Serum lead level was normal. Roentgenograms of the chest and skeletal survey showed no abnormalities. A bone marrow study showed myeloid hyperplasia only. Cultures for bacteria, fungi and tuberculosis were negative. Results of viral agglutinin studies and viral cultures especially for neurotropic viruses—including herpes simplex and coxsackie—were negative.

The patient was diagnosed as having coccidioidomycosis and it was decided to use intravenously administered amphotericin B and to not do cisternal injection but to give amphotericin B intrathecally by lumbar puncture. Intravenous administration of amphotericin B was started at 0.5 mg per kg of body weight every day and intrathecal administration at 0.5 mg every other day. The treatment plan was to continue giving amphotericin B intrathecally by lumbar puncture for a total dose of 15 mg, while gradually increasing the intravenous dose to 1 mg per kg of body weight. Acetylsalicylic acid, 180 mg four times a day, and trimethobenzamide hydrochloride (Tigan®), 100 mg capsules three times a day, were given to combat fever, vomiting and headache associated with amphotericin B administration. No other medications were used to tranquilize the patent and only a 1 percent solution of xylocaine was injected intradermally at the lumbar puncture site. To evaluate any toxic effects of amphotericin B, the patient's hematocrit, electrolytes, magnesium, creatinine, liver enzymes and urine were

monitored. After two weeks of therapy, the patient's hematocrit had fallen to 24; a transfusion of 200 ml of whole blood was given and the hematocrit increased to 32 and remained stable. Potassium supplements were started after eight days of therapy to stabilize serum potassium. After four weeks of therapy, while the patient was receiving 1 mg of amphotericin B per kg of body weight per day given intravenously, serum potassium levels had fallen to 2 mEq, and it was decided to stop amphotericin B for one day while the patient was given 40 mEq of potassium chloride intravenously. Following this, serum potassium levels rose to 3 mEq and intravenously administered amphotericin B was restarted at a daily dose of 0.75 mg per kg of body weight. Intrathecally administered amphotericin B was maintained at 0.5 mg every other day. Additionally, oral potassium supplements were increased to 40 mEq daily. The patient's clinical status continued to improve during the stay in hospital. Following the decreased amphotericin B dosage schedule, the hematocrit and potassium levels remained stable. At no time was the intrathecal administration of amphotericin B by lumbar puncture a technical or clinical problem. The child cooperated in the procedure and did not have any signs of irritation following injection. Examination of the cerebrospinal fluid after two months of therapy showed 24 cells, two thirds of which were lymphocytes. CSF glucose was 35 and CSF protein 23 mg per 100 ml. The patient's pleasant disposition returned, there was no irritability or lethargy and ataxia disappeared. Head circumference remained within normal limits. Repeated biweekly coccidioidymcosis skin tests showed only 1 cm of erythema and no significant induration at 24 and 48 hours.

The patient was discharged after two months of therapy, having received 30 intrathecal injections of amphotericin B for a total intrathecal dose of 15 mg. The total intravenous amphotericin B dose was 500 mg. After discharge, the patient received weekly injections of 0.5 mg amphotericin B in the spinal fluid and 9.5 mg intravenously.

After three months this dosage was given every other week for an additional three months. The therapy then was given monthly. Eighteen months after therapy was begun, amphotericin B was stopped. Complement fixation titers in the spinal fluid had remained negative during the 15 months of therapy, and sixteen months after cessation of therapy they have remained negative. Response to a coccidioidomycosis skin test became positive during the fourth month of therapy and currently is positive with 15 mm induration.

Clinically, the child had done well. Growth and development have been normal. There is no evidence of residual sequelae of meningitis or any signs of drug toxicity. The creatinine level was 0.6 mg per 100 ml and serum complement fixation was 3 plus at 1:8 for coccidioidomycosis.

Comment

Since the introduction of amphotericin B for parenteral administration in 1957, there have been numerous reports of its successful use in the treatment of patients with disseminated coccidioidomycosis.[1,2] The present case report shows that a child with coccidioidal meningitis can be successfully managed by a combination of intravenous and intrathecal (lumbar) administration of amphotericin B. Lumbar puncture administration was adequate to eradicate the disease and cisternal tap was not needed. Coccidioidal meningitis is one of the major causes of chronic granulomatous meningitis and, if untreated, is uniformly fatal. One must always consider this disease when there is an insidious onset of headache, nuchal rigidity and signs of confusion or drowsiness. Although this would apply especially to children residing in endemic areas such as California or the southwestern United States, with the widespread travels of families today, inquiries should be made about any temporary visit to endemic areas. Characteristically, examination of cerebrospinal fluid gives findings of a granulomatous meningitis with elevated protein, low CSF sugar and pleocytosis with mononuclear predominance. Most often the organism is not recovered from the cerebrospinal fluid and there usually are no other foci of coccidioidal infections observed. The diagnosis is confirmed by serological examination of the blood and spinal fluid for precipitating and complement fixing antibodies to coccidioides. A skin test usually gives negative results during dissemination of coccidioidmycosis and therefore is not a reliable sign of infection. A rising complement fixation antibody titer or a titer greater than 1:32 with a negative skin test, suggests dissemination of the disease or an imminent danger of dissemination and requires immediate therapy. Any complement fixation titers found in the cerebrospinal fluid are diagnostic of coccidioidal meningitis or extradural coccidioidal lesion because these antibodies do not usually cross into the CSF from the serum.[3]

During the course of therapy, a falling complement fixation antibody titer and a positive coccidioidal skin test indicate an excellent response to therapy and a favorable prognosis.

It is agreed that prolonged administration of amphotericin B is required to prevent recrudescence of the meningitis. In this case, therapy was given for 18 months. Amphotericin B in the serum does not pass the blood-brain barrier in adequate amounts, but it may mask meningitis during intravenous treatment. All children with signs of disseminated coccidioidomycosis should have a lumbar puncture done before receiving amphotericin B since early treatment directed against the central nervous system infection is mandatory. Coccidioidal meningitis must be treated by intrathecal administration of the drug. Doses of 0.5 mg every other day are often necessary. Concurrently, amphotericin B is given intravenously starting at a low dose (0.25 mg per kg of body weight) and increasing to 1 mg per kg of body weight if tolerated. The patient reported here tolerated only 0.75 mg per kg every other day.

Recently, Glynn and coworkers reported the use of intrathecal (lumbar) administration of amphotericin B with hyperbaric glucose and stressed the dangers of cisternal tap; before the present report, intrathecal administration of amphotericin B was felt to be effective only when given by cisternal puncture or the use of an intraventricular reservoir.[4-6]

It is noteworthy that the child reported in this case history was treated by repeated lumbar punctures without any special solutions and this offered no technical problems. The child was given only acetylsalicylic acid and trimethobenzamide hydrochloride medication. Arachnoiditis was not noted, and the response to therapy was excellent.

Summary

A 2¾-year-old boy was coccidioides immitis meningitis was successfully treated by the combined use of amphotericin B given intrathecally by lumbar puncture and intravenously over an 18-month period. Cisternal tap was not needed to eradicate the infection. Clinical improvement was pronounced and no serious complication of therapy was encountered. Sixteen months after cessation of therapy, the patient remains in excellent health with no evidence of residual disease or damages.

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LETTERS *to the Editor*

Pupil Size in Heat Stroke

To the Editor: In the excellent Medical Staff Conference review of heat stroke (West J Med 121:305-312, Oct 1974), the patient described in the case summary was observed on initial physical examination to have dilated pupils. Although this finding has been reported by others, in a retrospective study of six patients treated at the San Francisco General Hospital for heat stroke between 1962 and 1974, three were found to have had pinpoint pupils on admission. Five of the six patients arrived in the Emergency Room comatose. Two of the six patients died and four of the six experienced lengthy and complicated clinical course. Three patients developed disseminated intravascular coagulopathy and two experienced focal seizures. Decerebrate posturing was also noted in two of the three patients with pinpoint pupils; diarrhea was observed in all three.

The mechanism of these variable pupil effects is unknown and, despite the numerous studies on heat stroke, we could only find one study which had made any consistent observations of pupil size.[1] In this study of thirty patients, five had pinpoint pupils, seven had dilated pupils, and eighteen had normal sized pupils. In the patients with pinpoint pupils a positive association between deep coma and a high temperature on admission was made.

Therefore, from our limited experience with heat stroke and the somewhat meager evidence in the literature,[1,2] we feel that heat stroke must be included in the differential diagnosis of any comatose patient presenting with constricted pupils.

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More on Oral Contraceptives

To the Editor: Swerdloff et al have presented a most impressive article, "Complications of Oral Contraceptive Agents—A Symposium" (Swerdloff RS, Odell WD, Bray GA, et al: West J Med 122: 20-39, Jan 1975). Attention should be called to the complication of oral contraceptives that they did not discuss and which is highly relevant clinically. The complication I refer to is that of emotional disturbance—primarily depression. As early as 1967[1] oral contraceptives were implicated in causing significant emotional disturbance and in 1968 several authors[2,3] called attention to the association of oral contraceptives and depression. Given the large number of women at risk even a very low incidence of oral contraceptive related depression becomes an important issue. Given reported figures of 6.6 percent[4,5] of women developing depression on "the pill" the matter assumes major importance. A series of studies have questioned this[6,7] or placed it in the "psychological" realm[8] yet, recent evidence seems to clearly indicate that for some women (especially those with a history of depressive disorder or depression during pregnancy) oral contraceptives will reactivate depressive symptoms. That evidence has been found primarily in the British literature[9-11] and indicates clearly that trytophan metabolism is altered in some women while on oral contraceptives, is associated with relative or absolute pyridoxine deficiency, and is accompanied by depressive signs and symptoms. Further that treatment of depressed women taking oral contraceptives and found to be vitamin B_6 deficient with supplementary pyridoxine significantly relieved depressive symptoms in all cases. Bray in his discussion covers Spellacy's work on carbohydrate metabolism well but necessarily did not include his work on B_6 metabolism.[12] In any case, some women on oral contraceptives will develop pyridoxine deficiency and clinical depression and this requires our attention as physicians—especially since the response to treatment is impressive.

An excellent review article by Winston can be found in the *American Journal of Psychiatry* 130: 1217-1221, November 1973.

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Medicine and Religion

TO THE EDITOR: Though there will undoubtedly be some who will disagree with your editorial (The clergy and patient care. West J Med 121:498-499, Dec 1974) it is a truism "that there is much the clergy can contribute to patient care."

Perhaps, the only disappointment to one who totally agrees with your suggested roles for the clergy is the absence of any suggestion to reactivate its involvement in moral guidelines. This is particularly so in the present climate of amorality which is linked directly to VD incidence. Almost all presentations about VD disguise from the public the realities of what is happening and ignore the moral issues. No other presentation than the TV production "VD Blues" has so successfully driven home the bankruptcy of significant present-day solutions to our permissiveness.

It seems reasonable to suggest that, if any inroad is to be made in decreasing the incidence of VD, the customary (but inadequate) public health approaches should be only one portion of the attack on VD. The attack should draw its main inspiration from morality with the positive and active utilization of the clergy. To banalize religion by regarding VD as a private matter with no behavioral implications is to lose a valuable ally. This, to some, is archaic or old fashioned ("Victorian"). Yet, its effectiveness in former decades was known in our society when we were more responsive to "old" values.

Admittedly, the prestige of religion is at a low, currently. A new emphasis on the medical disadvantages of immorality would nudge the clergy. Since the old-fashioned moral guidelines were and still are based upon a sound medical foundation, morality would draw strength and conviction from medicine. That makes sense.

In recent years, we have been repeatedly told to "treat and not moralize." Such advice contributed momentum to the exhaustion of our moral environment and peopled our present generation of physicians with too many dehumanized practitioners. Emphasis on the adverse medical effects of current life-styles is good medical advice, not censure or moralizing.

There have been, in the last two to three years, a few small gratifying signs, here and there, of the medical profession speaking in behalf of the beneficial aspects of morality. It is particularly encouraging that *The Journal of the American Medical Association* (228:1117-1119, May 27, 1974) included in its pages E. Gray Dimond's commentary on the physician's role as a moral persuader. The cry for such a role is an old idea—resurrected, like numerous ones, from past medical history.

There is much that we can learn to our profit from the present medical crises. The tragic situation should make clear to us that morality is an asset of inestimable medical value to the preservation of our social fabric. Our active participation may even have a salutary indirect effect in stemming the inroads of state medicine.

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Trauma Rounds

Chief Discussant
OSCAR SALVATIERRA, MD

Editors
DONALD D. TRUNKEY, MD
F. WILLIAM BLAISDELL, MD

This is one of a series of Conferences on Trauma at San Francisco General Hospital

Refer to: Salvatierra O: Management of urologic injuries (Trauma Rounds). West J Med 122:257-261, Mar 1975

Management of Urologic Injuries

JOHN SNEAD, MD:* The patient for presentation today is a 6-year-old boy who was run over by a large bus. He sustained severe crushing injuries to the lower abdomen and pelvic region. The initial evaluation at San Francisco General Hospital showed a blood pressure of 60/20 mm of mercury with poor peripheral perfusion. The abdomen rapidly became distended. The pelvis was grossly unstabile and there was penile bleeding. Attempts to pass a Foley catheter were unsuccessful. Rectal examination revealed a flaccid sphincter and a free-floating prostate. After resuscitation with 1,000 ml of Ringer's lactate an intravenous pyelogram was obtained which showed a normal kidney on the right side. The upper pole of the left kidney was poorly visualized and the lower pole was not seen.

On immediate laparatomy, extensive injuries were found. These included a ruptured left hemidiaphragm, ruptured spleen and a hugh retroperitoneal hematoma extending from the pelvis to both diaphragms. The bladder was separated from the urogenital diaphragm by a distance of over four inches. Operative treatment consisted of repair of the diaphragm and removal of the spleen and left kidney. The pelvic hematoma was not entered. The bladder injury was treated by suprapubic cystostomy and suprapubic drains, which was accomplished without entering the retroperitoneal hematoma.

During operation there was cardiovascular instability and 11 units of whole blood were administered. Postoperatively, all of the wounds continued to bleed and results of coagulation tests showed a prothrombin time of 17 seconds, and a partial thromboplastin time of greater than 100 seconds. Fresh, warm blood was obtained through a special program with Irwin Memorial Blood Bank. After administration of this blood and eight platelet packs, the oozing ceased. Two more units of whole blood were administered slowly over the next 24 hours. The pelvic fractures which included acetabular displacement were treated by skeletal traction with a tibial pin.

The postoperative course was stormy and marked by respiratory failure, mild renal failure and mild elevation of serum bilirubin. This reached a peak at six days after injury. Since that time the patient has progressively improved and is doing well at this time two weeks after injury.

DONALD D. TRUNKEY, MD:† *We have asked Dr. Oscar Salvatierra to discuss this patient and give his approaches to treating urologic trauma.*

OSCAR SALVATIERRA, MD:‡ This patient provides an example of what I also found in my Vietnam and civilian experience. A large percentage of

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urological injuries are associated with other abdominal and chest injuries. These other major organ system injuries are usually the more obvious and usually assume a higher priority for treatment. This is an essential point, as it emphasizes that treatment of the urological injury must be correlated with the management of the associated problems.

In a severely injured patient, such as the one presented here, a short time invested in intravenous pyelography, will provide essential information about the contralateral kidney if nothing else. In this case the primary renal injury involved the left kidney and I understand there was extensive fragmentation and hemorrhage from the renal substance. Nephrectomy was the proper treatment, especially in the context of the other injuries and since the right kidney was normal. Attempts at repair of the left kidney would have only resulted in the risk of additional hemorrhage, intraoperatively and postoperatively, and prolongation of the operating time.

The same principles hold true in the management of the severed membranous urethra and associated massive pelvic hemorrhage in this patient. The treatment of choice in this case was suprapubic cystostomy without any attempt at urethral approximation. Violation of the large contained retroperitoneal hematoma would have risked extensive hemorrhage from the injured pelvic veins. I shall make additional comments relative to the urethral injury later in the presentation.

A good dictum in the treatment of renal injuries is that nonoperative treatment should be chosen whenever possible. However, conservative management requires proper radiographic assessment of urinary tract anatomy. Intravenous pyelography, especially infusion nephrotomography, can best be accomplished after the treatment of shock. At this point definitive radiographic investigation should be initiated if there is a possibility of renal injury, unless prohibited by the need for urgent surgical intervention for associated life-threatening injuries. In many instances, x-ray studies of the abdomen will be required in a badly injured patient, and it is relatively easy to give the patient contrast material before these films. Any information which is obtained may be of value, if only to provide information that the opposite, uninjured kidney is functional.

If the intravenous pyelogram (IVP) shows diminution in renal contrast excretion or minimal delay in the appearance of contrast material, as opposed to that of the opposite kidney, contusion is implied. At the other end of the spectrum, nonfunction indicates either severe renal fragmentation or renal pedicle injury and demands either urgent arteriographic assessment, or exploration as dictated by the patient's clinical situation. One instance in which intravenous pyelograms may be normal but still associated with major renal injury is in certain types of penetrating wounds to the kidney in which there may be an arteriovenous fistula. If persistent hematuria is present, early arteriography in addition to pyelography should be considered to rule out some type of major vascular injury.

My principal indication for exploring renal injuries is the presence of an expanding flank mass or an expanding or pulsatile perirenal hematoma noted at laparotomy. In addition, if there is clinical evidence of continuous hemorrhage after transfusion of three units of whole blood, surgical exploration should be strongly considered. Other indications for exploration relate to the extent of injury as noted on x-ray examination. Severe fragmentation of the kidney with loss of the renal architecture, a renal pedicle injury or a ureteral injury, are indications for surgical treatment.

More patients with penetrating renal injuries will require exploration than patients with renal injury secondary to blunt trauma. Approximately 85 percent of nonpenetrating renal injuries are simple contusions or superficial lacerations. All of these patients should be treated conservatively. About 5 percent of blunt renal injuries are of such severity that operative intervention is indicated for control of life-threatening hemorrhage. Then there is a group of about 10 percent with moderately severe renal injuries that require careful observation. A conservative treatment plan is continued as long as the flank mass remains stable, the patient does not manifest continuing volume loss clinically, and hematuria is transient or mild.

F. WILLIAM BLAISDELL, MD:* *Dr. Salvatierra, how significant do you think urinary extravasation is to the hazard of subsequent infection? Many argue for routinely exploring the kidney when there is any evidence of injury. The basis of this is that secondary complications, such as infection with or without secondary hemorrhage, will be a greater threat to the patient than the exploration itself.*

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DR. SALVATIERRA: I do not routinely explore and drain all urinary extravasations and do not believe that the risk of infection is very great. Urinary extravasation secondary to penetrating trauma carries with it the possibility of ureteral injury and all ureteral injuries demand early exploration and repair. In blunt trauma, mild to moderate extravasation confined within Gerota's fascia may be initially managed conservatively, particularly if ureteral decompression is satisfactory. However, voluminous extravasation of sterile urine, or minimal infected extravasation, can result in septic complications initially, or subsequently may lead to retroperitoneal cicatrization and ureteral obstruction.

DR. BLAISDELL: *You would be guided by the* IVP?

DR. SALVATIERRA: Yes, primarily by the extent of the extravasation and whether or not it is confined by Gerota's fascia.

A PHYSICIAN: *I would like to ask a question about long term complications. When you treat renal injuries conservatively, do problems such as renal hypertension or chronic renal failure develop later?*

DR. SALVATIERRA: Renal failure is essentially nonexistent following renal injury. The only time this possibility is apt to occur would be in a major injury to a solitary kidney, or in rare cases of bilateral severe injury. Although the incidence of hypertension following renal injury is very low, it does occur and long term follow-up of the patient is necessary. Hypertension can be the result of ischemia in a damaged renal segment, renal artery stenosis, or possibly the constricting enveloping effect from a cicatrizing subcapsular hematoma, the so-called "Page" kidney.

A PHYSICIAN: *What is your policy regarding retroperitoneal hematoma if you have not obtained a pyelogram before laparotomy?*

DR. SALVATIERRA: I use the same criteria for exploration of this hematoma as if I had a pyelogram. In other words, I would adopt a conservative approach if the hematoma was stable, nonexpanding, nonpulsatile and appeared to be contained. However, if exploration is deemed necessary, it is imperative to have information about the status of the opposite kidney. Here the advantages of a preoperative pyelogram become evident. The reason, of course, is that if the surgeon opens the fascia enclosing the kidney, severe hemorrhage may ensue from an untreatable venous hilar injury which may require nephrectomy.

DR. TRUNKEY: I would underscore that policy, which is the one we had adopted at this hospital. I would like to point out, however, that any central hematoma which is associated with the duodenum or pancreas is explored routinely. Dr. Salvatierra is talking about the lateral or flank hematoma. The only difficulty we encounter is always being able to tell which organ the hematoma is associated with, as flank hematomas may merge with central hematomas.

DR. SALVATIERRA: An additional point I would like to make is that not all patients with urological injuries will present with obvious hematuria. Hematuria may be absent in parenchymal renal trauma, renal pedicle injuries and ureteral injuries. In any patient with blunt or penetrating injury to the chest, abdomen or back, a high index of suspicion for possible urological injury should exist.

This leads me to ureteral injuries, which of all urological injuries are the most apt to be missed initially. Ureteral injuries are difficult to diagnose preoperatively unless an intravenous pyelogram has shown obvious urinary extravasation. Ureteral injury is unusual following blunt trauma but must be considered a possibility following penetrating trauma. A ureteral injury should be suspected whenever a missile track passes near the ureter. In such cases it is preferable to isolate and inspect the ureter at laparotomy. The injection of indigo carmine intravenously may be helpful intraoperatively if any doubt exists about ureteral injury and will help localize the site of injury.

Certain principles of repair are especially important in the management of ureteral injuries. Bullet injuries of the ureter result in large ragged defects, with considerable surrounding tissue damage. Because the ureter will not heal properly if necrotic tissue is interposed, the injured area should be completely resected (even in partially transected ureters). Each free end of ureter should then be spatulated so that an elliptical end-to-end anastomosis can be accomplished. Concentric constriction of the anastomosis is thus avoided. It is also important that tension be avoided at the suture line, and that the ureteral blood supply be preserved by not stripping ureteral

adventitia. I prefer to use stents only for alignment and position of the ureter in those patients with a badly traumatized retroperitoneal space. In most instances, the use of a foreign body in the ureter such as a T tube or ureteral catheter only increases the risk of anastamotic leak.

Almost all bullet injuries of the ureter may be handled in this manner, except those adjacent to the ureterovesical junction, where a ureteroneocystostomy can often best be done. In rare instances where ureteral loss is extensive, consideration can be given to ureteroureterostomy using an anastamosis to the contralateral ureter or—even more rarely—to autotransplantation of the kidney. Decisions such as these will be based on the condition of the patient and the associated injuries.

A Physician: *Dr. Salvatierra, what do you do with the missed ureteral injury?*

Dr. Salvatierra: The principal signs of delayed recognition of a ureteral injury include: urinary fistula through the surgical wound, drain site or bullet wound; massive urinary acites; abscess, and stricture associated with urinary extravasation. It is thus understandable why late recognition of a ureteral injury carries with it a greater than 40 percent incidence of secondary nephrectomy. When there is delayed recognition of the injury, there is usually extensive tissue induration or infection in the area where primary ureteral anastomosis might be accomplished. In these cases, it is important to establish good urinary drainage above the area of injury, such as with a nephrostomy, and not attempt to reestablish ureteral continuity until a later date.

Complete disruption of the posterior urethra is a serious injury and its management has evoked much controversy. The method of treatment employed in this case is that advocated by Johanson and MacKinnon. In this approach urethral continuity is established by delayed elective urethroplasty after initial simple cystostomy. Delayed elective urethroplasty can later be carried out with ease and with the presence of remarkably little scar tissue. The striking feature of simple cystostomy followed by delayed elective urethroplasty is that the incidence of stricture, incontinence and impotence appears to be much lower than that following conventional treatment which establishes uretheral continuity immediately after injury. The latter method should probably not be employed if it requires opening a large contained retroperitoneal pelvic hematoma. This consideration is of paramount importance in the presence of severe associated injuries such as in the case presented today.

If the surgeon who explores the severed membranous urethra is experienced in handling this type of lesion, if the pelvic hematoma is not large and if the urethral injury is the principal problem, direct approximation of the severed urethra can be carried out. When I have followed this approach, I have used Vest perineal sutures for the approximation. Direct suture approximation of the urethra is difficult and attempts at this type of procedure only result in additional tissue damage with subsequent increased scar tissue in the area. Traction on the Foley balloon catheter

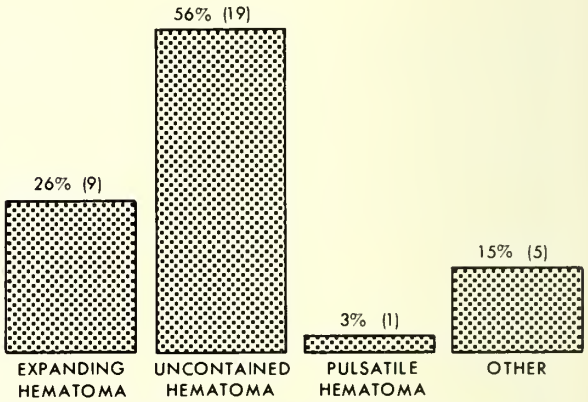

Chart 1.—Reasons for opening Gerota's fascia in 34 patients.

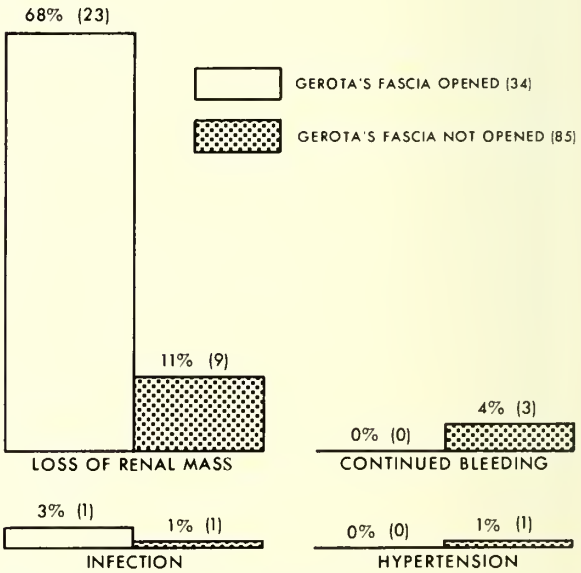

Chart 2.—Postoperative complications in 119 cases of renal trauma.

should not be employed as this may damage the bladder neck and cause postoperative incontinence.

If it appears that the membranous urethra injury is an incomplete rupture, rather than complete membranous-prostatic urethral dismemberment, then simple cystostomy alone should be done. Several weeks after partial disruption, managed in this fashion, the cystostomy tube can be clamped. If normal micturition is demonstrable through an intact nonstricture urethra with a voiding urethrogram no further treatment is required.

DR. TRUNKEY: We are in complete agreement on the management of urologic trauma as you have reviewed it. Drs. Holcroft, Lim and myself recently reviewed the cases of renal injury treated at this hospital during the last 10 years. In 140 of these cases, there was definite definition of renal damage. Confirming your earlier observation, 8 percent had no hematuria. Of the 140 patients, 34 (24 percent) had Gerota's fascia opened for the reasons you outlined, that is, a uncontained hematoma, expanding hematoma or pulsatile hematoma (Chart 1). There was a very high incidence of nephrectomy (56 percent) in those patients where Gerota's fascia was opened. In contrast 106 of the 140 cases were followed conservatively. In six of these patients exploration subsequently was done for either nephrectomy or partial nephrectomy. There was minimal postoperative morbidity in the rest of these patients managed conservatively. Data for 85 of these patients are shown in Chart 2. There was a single instance of hypertension in these patients.

Refer to: Bush JW, Chen MM, Bush AS: No-fault malpractice insurance—Proximate cause and the quality of medical care (Medical Jurisprudence). West J Med 122:262-270, Mar 1975

No-Fault Malpractice Insurance

Proximate Cause and the Quality of Medical Care

J. W. BUSH, MD, M. M. CHEN, PhD, *and* A. S. BUSH, MS, *La Jolla*

No-fault medical malpractice insurance has been proposed as an alternative to the present tort liability approach. Statistical examination of the concept of proximate cause reveals not only that the question of acceptable care, and therefore of fault, is unavoidable in identifying patients deserving compensation, but also that specifying fault in an individual case is scientifically untenable. A simple formula for a Coefficient of Causality clarifies the question of proximate cause in existing trial practices and suggests that many of the threats associated with malpractice suits arise from the structure of the tort-insurance system rather than from professional responsibility for medical injury. The concepts could provide the basis for a revised claims and compensation procedure.

THE BURDEN of high insurance fees, the threat of lawsuits and the increasing acceptance of no-fault automobile insurance have made many medical practitioners consider alternatives in insurance plans to cover medical malpractice. The goals of any malpractice insurance system should be to compensate in a just and equitable manner all those incurring negligent medical injuries and to serve as a stimulus to improving the quality of medical care. But retaining any form of compensation identifying negligence preserves the concept of fault. Spreading the risk through insurance, however, virtually abandons the concept of individual fault and accepts the notion of collective professional responsibility for compensating victims of substandard treatment.[1]

Our purposes are to use statistical methods to clarify discussion and judgment on the proximate cause of a disability and to find a basis for using the forces inherent in malpractice insurance to improve the quality of medical care. Our research into the measurement of health care outcomes[2,3] suggests that a probabilistic framework for analyzing the issues of malpractice insurance may provide the basis for a more efficient and equitable compensation system divorced from the concept of individual fault.

Our emphasis in this analysis will be on proximate cause, and we will not directly discuss several other important matters, such as (1) criteria for determining the standard of care, (2) criteria for determining the presence or absence of a disability or (3) other issues such as informed consent or abandonment. While acknowledging these questions as proper and legitimate grounds for debate, we will assume that they have all been

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resolved and that the question of proximate cause remains. This strategy will permit us to show the independence of proximate cause from the other questions and to work out the implications of proximate cause for various insurance schemes.

Probabilities and the Law

Objective or historical probabilities refer to the fraction of times a particular event will tend to occur in a large number of similar situations. For example, the percentages cited from recorded series of clinical cases form one of the bases for clinical judgments by indicating the prognoses that will apply in various disease or treatment situations. These probabilities are verifiable in the real world and, using statistical methods, valid inferences can be made to a universe from a particular probability sample. Such data are acceptable to the courts; the main legal question concerns the relevance of the data to the case at hand.[4]

Subjective probabilities, on the other hand, are widely used among decision theorists as a measure of certainty or degree of belief. Such uses, stemming especially from the work of Savage,[5] are controversial even among statisticians. A major characteristic of such probabilities is that they apply to single events. Not surprisingly, given the pressure of a trial, experts have occasionally testified that they are "90 percent certain" that a treatment did or did not result in the alleged damage. This would be a subjective probability in statistical or decision theory terms. The expression cannot be understood as applying either to a confidence interval or to a proportion of historical cases —the usual meanings of percentages and probabilities in medicine and science; on appeal, such judgments were considered speculation that should not be treated as quantitative evidence.[6]

Bayes' theorem, another statistical technique, has also been used in the legal setting. Given an outcome in a malpractice case, and relevant "prior" probabilities, Bayes' theorem will give the probability that a particular treatment was used. Courts have held, however, that determining history by probabilities is inadmissible since more direct evidence should exist on historical events.[7] This is especially true in malpractice litigation where we usually know the treatment used, and the trial questions its appropriateness and causal relation to the outcome (disability). Thus, Bayes' theorem yields superfluous information in malpractice litigation.[8] This paper will contain no further discussion of Bayes' theorem or subjective probabilities.

For objective probabilities, two estimation procedures are available. The first, direct statistical inference from a random sample to its universe, is highly desirable, but impractical and infrequent in medical malpractice litigation.

The second procedure is expert estimation. This is based on historical probabilities and is similar to them in principle. This procedure is applied to a case at hand through a queston about a hypothetical case for which no *identical* relative frequency exists. But a similar series could exist, and, in fact, may actually exist in the expert's knowledge and experience. Therefore, expressing a judgment about outcomes in *a large number* of cases *like* the plaintiff's in all important aspects is precise and legitimate.

Medical Experts as Witnesses

In malpractice, proof of departure from accepted medical practice is not enough; the departure must be the proximate cause of the injuries claimed.[9,10] The statistical problem is to abstract from a stream of events the effects of a difference between two treatments, recognizing that different treatments do not change outcomes themselves, but only the relative frequencies of outcomes in large series of cases.

Also, in view of the complexities of disease histories, it is not enough for a medical expert to testify about the facts and let the judge and jury interpret them. Where personal injury is involved, the medical expert must interpret the facts for them; he must render a judgment about the causal relation. Experts who are legally qualified to present statistical evidence are also legally qualified to combine the probabilities and draw inferences from them. Court rulings clearly indicate that, where statistical evidence exists for individual probability factors, probability theory is acceptable for induction and inference.[11]

Using probability theory for induction is not the same, however, as providing a "measure of proof."[8,12,13] Even when probabilities are known and computed precisely, a serious question remains. Many malpractice cases stand in the region of uncertainty between 10 and 90 percent, and a decision must be made. But instead of specifying the exact degree of certainty sought, the law uses a variety of terms to describe the cutoff point.

The simple "possibility" that injury resulted from the act is not of sufficient "probative value";

it must be a "probability" to be of reasonable "medical certainty."[14] But "reasonable medical certainty" might mean a probability of 85, 90 or even 95 percent. What is meant by the "preponderance of the evidence"? Does it mean, in malpractice as in other cases of civil law, at least 51 percent accuracy in making judgments?[15] Definitive court rulings are lacking, and every juror has his own reaction to the statistics.

Although courts realistically recognize the statistical nature of causal relations, especially in clinical and experimental science,[16] the effect of not specifying a "measure of proof" is to simultaneously ask the medical expert not only the probability of a bad outcome in a particular type of case, but also his own arbitrary cutoff point for accepting causal relations. Herein lies a conflict between medical and legal standards of "proof."

On the contrary, percentages reported on series of cases similar to the plaintiff's are admissible by the courts.[17] Such reports are what the expert knows best, and we would like to construct a rigorous concept of causality on such relative frequencies or objective probabilities. We will then return to the measure of proof.

Conceptual Definition of Proximate Cause

The possibilities in medical negligence can be diagrammed as shown in Figure 1.

Ideal evidence on causality comes from completely controlled experiments with all possible causes of change except the treatments held constant through randomization. Assume a controlled experiment with 200 subjects randomly allocated between two treatments—an alleged negligent treatment R_1 and an alleged acceptable treatment R_0. The relative frequency of the two outcomes, the specific undesirable outcome D_1 and absence of specific undesirable outcome D_0, could then be shown as follows:

	Outcome		
	Disability	No Disability	
Treatment	D_1	D_0	Total
"Negligent" R_1	50(a)	50	100
Accepted R_0	20(b)	80	100

Cell (a), the total number (or proportion) of patients with disability D_1 after "negligent" treatment R_1, consists of two components: the 20 persons (equal to b) who would have the disability even with acceptable treatment R_0, plus the 30 persons in excess of the 20 (a minus b) that are attributable to R_1. Thus, of all patients in (a), only a fraction are there because they were treated with R_1. Considering all other factors equal or irrelevant, that fraction expresses precisely a coefficient of proximate causality:

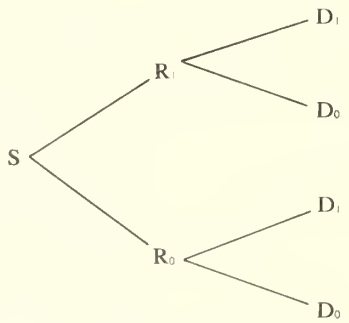
$$C = \frac{a-b}{a} = \frac{50-20}{50} = \frac{30}{50} = .60 = 60\%$$

In long series of outcomes D_1 following treatment R_1, that is, long series of cases in cell (a), 60 percent may be attributed to R_1.

As we shall discuss later, the number of cases alters the range of error in estimating the mean proportions (a) and (b), and therefore alters the results of significance tests. As long as the total number of cases in the two rows (R_1 and R_0) is equal, however, the number of cases does not alter the basic structure of the causal relation (C).

Outcomes in (a) attributable to the negligent treatment must be identified and separated unless all disabilities in both (a) and (b) are to be compensated. Since disease and injury or the unavoidable risks of proper therapy produce most bad outcomes, compensating both (a) and (b) in a nonfault plan from professional liability resources means that, contrary to the principles of tort law, sources of compensation bear no relation to sources of injury.[18] Limiting compensation to patients in (a) does not resolve the problem, because a standard of care and therefore fault must be established to differentiate acceptable or nonacceptable treatment, and because many in (a) would have suffered the disability under either therapy.

On the other hand, compensating patients in



S = the situation ("state of nature") before medical intervention

R_1 = an alleged negligent treatment
R_0 = an alleged acceptable treatment
D_1 = the presence of a specific undesirable outcome (disability, disease, discomfort, death)
D_0 = the absence of the specific undesirable outcome

Figure 1.—Diagram of the possibilities and outcomes of medical negligence.

(a) whose disability resulted from negligent treatment would be just. But even with a perfect experiment, separating individual patients in (a) whose bad outcomes resulted from the treatment in the individual case is not only unknowable, but cannot be given a scientific meaning. The nature of scientific knowledge and disease processes forces us to conclude that causality cannot be given an operational definition in a *particular* case.

Establishing a standard of professional care to limit the compensation to patients whose outcomes *may* be the result of treatment means that the concept of fault must be preserved. That is, no outcome criteria can exist for compensation without identifying a deviation from acceptable medical practice. Unlike automobile insurance, the risk situation is asymmetrical. The physician is not at risk of personal injury by the behavior of the patient, so the liability is not balanced among competing insurance companies in the long run. The carrier's recourse is to cancel the physician's insurance, introduce merit rating or take some other action to reduce its liability. The threat is to the physician who must risk practice without insurance.

We will explain further the properties of the Coefficient of Causality (C) before discussing its relation to the measure of proof, its application in the current court situation and its implications for alternative insurance schemes.

Operational Definition of Proximate Cause

Let us still assume that we are using data from a randomized experiment designed exactly to test the plaintiff's case. In the following examples, the negligent treatment R_1 appears in the first row, the disability D_1 in the first column and the absence of disability D_0 in the second column; the plaintiff's case is in the upper left corner (a):

	D_1	D_0	*Total*
R_1	55(a)	45	100
R_0	5(b)	95	100

$$C = \frac{a-b}{a} = \frac{55-5}{55} = \frac{50}{55} = .91 = 91\%$$

The coefficient indicates that the "negligent" treatment (R_1) would be the major causative factor in 91 percent of a long series of cases disabled like those in (a). The rare extreme of certainty occurs when the disability does not occur at all with the acceptable treatment, but may occur with the "negligent" treatment:

	D_1	D_0	*Total*
R_1	5(a)	95	100
R_0	0(b)	100	100

$$C = \frac{a-b}{a} = \frac{5-0}{5} = \frac{5}{5} = 1.0 = 100\%$$

The probabilities strongly suggest that R_1 caused D_1, all other things being equal. This situation does *not* suggest res ipsa loquitur, however, since such differences may occur between two acceptable treatments, as will be discussed later. Res ipsa could apply only when the outcome in question did not occur after *any* acceptable treatment.

The opposite extreme from certainty is represented by:

	D_1	D_0	*Total*
R_1	50(a)	50	100
R_0	50(b)	50	100

$$C = \frac{a-b}{a} = \frac{50-50}{50} = \frac{0}{50} = 0$$

Such evidence requires rejection of the hypothesis that the treatment caused the disability. The disability in question occurs no more frequently with the alleged negligent action than without it.

Outcomes need not be equally likely to refute the idea of a causal relation:

	D_1	D_0	*Total*
R_1	33(a)	67	100
R_0	33(b)	67	100

$$C = \frac{a-b}{a} = \frac{33-33}{33} = \frac{0}{33} = 0$$

As the specific disability D_1 becomes less likely with the standard treatment, the coefficient becomes more sensitive to deviations from standard practice:

	D_1	D_0	*Total*
R_1	15(a)	85	100
R_0	5(b)	95	100

$$C = \frac{a-b}{a} = \frac{15-5}{15} = \frac{10}{15} = .67 = 67\%$$

Even though the disability occurs in only 15 percent of persons treated with R_1, since it occurs in only 5 percent of persons receiving R_0, in the *long run* 67 percent of those with D_1 following R_1 can be attributed to the negligent treatment. The coefficient is much less sensitive (as it should be) where the disability occurs frequently with acceptable treatment:

	D_1	D_0	*Total*
R_1	95(a)	5	100
R_0	85(b)	15	100

$$C = \frac{a-b}{a} = \frac{95-85}{95} = \frac{10}{95} = .105 = 10.5\%$$

Given a disability D_1 following R_1, the probability is only 10 percent that it was due to negligence. Nevertheless, in a long series of people treated negligently, 10 percent more would suffer the disability than with the acceptable treatment.

In the concept of proximate cause outlined here, all the disabilities D_1 due to factors other than the negligent act R_1 are measured by the number of cases subsequent to the acceptable treatment. When these constant outcomes are subtracted from the cases of D_1 subsequent to R_1, it leaves the net effects attributable to R_1. Thus, when the legal question is framed in matrix form, the Coefficient of Causality (C) is a direct expression of the likelihood of proximate cause.

Since doing a controlled experimental trial for each malpractice claim is impossible, expert estimation based on prior experience is the accepted, and the only, alternative. The expert can conveniently answer the question of proximate cause by constructing a two by two category matrix of results based on his knowledge and clinical experience. He should construct the framework and cite probabilities as nearly as possible to cases like the one being tried. Relevance to the case is the most important question.[4]

In malpractice litigation, multiple disabilities are frequently alleged to result from multiple negligent acts.[10] Such cases represent more difficult legal and statistical problems. An important result of such an analysis is that a treatment cannot be considered improper medical practice simply because a disability may result. Consider two treatments with possible injurious outcomes, but outcome D_2 after R_2 more severe than D_1 after R_1. R_1 is then acceptable treatment with a known risk of incurring D_1. If a patient treated appropriately with R_1 suffers D_1:

	D_1	D_2	D_0	*Total*
R_1	5(a)	0	95	100
R_2	1(b)	4	95	100

$$\text{then } C = \frac{a-b}{a} = \frac{5-1}{5} = \frac{4}{5} = .80 = 80\%$$

But if R_1 is accepted medical practice, then the probability of incurring D_1 is a risk of proper treatment considered less important than avoiding D_2. Although informed consent might be questioned, the existence of *both* a disability *and* a causal relation to therapy is not direct evidence of malpractice, even though the injurious outcome may be rare.

Treatment acceptability depends on *separate* testimony about the standard of care. Such testimony considers both the probabilities and the *relative importance* of all the consequences of all the treatments. Assessing the relative importance of different outcomes is not nearly as straightforward in decision theory as combining probabilities, so we have limited our formal analysis to the single disability alleged by the plaintiff. In fact, many treatments may be acceptable simply because, all things considered, the set of outcomes from any one treatment may not be clearly superior to the set of outcomes from any of the other treatments. In a particular case, however, the treatment given may have been unacceptable; the issue of a standard of care is unavoidable *before* a Coefficient of Causality is computed.

Statistical Significance Tests

Introducing standard tests of statistical significance complicates the issue still further. Statistical significance depends, not only on differences in probabilities of different outcomes, but also on the number of similar cases (amount of experience) on which the differences were computed. Since experts almost always respond to hypothetical questions about a sample of cases similar to the plaintiff's, postulating very large samples, say 1,000, eventually makes all outcome differences statistically significant; postulating very small samples, say 10, makes most differences insignificant. Furthermore, no precise, commonly used statistical test exactly fits the question posed in malpractice litigation.

Standard tests do, however, give important insight. As a basis for the expert's judgment, let $n_1 = 100$ be the "negligent" treatment sample size and $n_0 = 100$ be the "accepted" treatment sample size. Applying large sample tests for differences among proportions[19] gives the results shown in Table 1.

With cases in court, bad outcomes from negligent treatment are probably higher than from accepted treatment, so a one-tailed critical region should be used; with the significance level α at 5 percent, the normal deviate z_α is 1.64. This cutoff point accepts the statistical significance of differences in cases 1, 2, 5, and 6 (Table 1); the hypothesis of no difference is not rejected in cases 3 and 4. Where the difference in bad outcomes is not statistically significant, the case for causality by the "negligent" treatment fails. So the tests should be applied *before* computing the probabilistic degree of causality (C); computing C is

TABLE 1.—*Results of Applying Large Sample Statistical Significance Tests for Differences Among Proportions (See text).*

Case	*"Data"*		*z-statistic*	*Result*	*C-Coefficient (Percent)*
1	55	45	7.72	Significant	91
	5	95			
2	5	95	2.26	Significant	100
	0	100			
3	2	98	0.58	Insignificant	50
	1	99			
4	55	45	0.35	Insignificant	10
	50	50			
5	15	85	2.36	Significant	67
	5	95			
6	95	5	2.36	Significant	10
	85	15			

inappropriate if the statistical tests are not significant.

Statistical tests are complementary to, and do not substitute for, testimony about the standard of care. Even if the treatment given is *not* acceptable care, a particular bad outcome (the plaintiff's) may not occur sufficiently more frequently to warrant a judgment. The z statistic, or the equivalent Chi-square, applied to relevant experience, tests that hypothesis. The denominator (n_1, n_0) should be set according to the order of magnitude of the relevant experience, say 10 for rare treatments, 100 for more frequent treatments and 1,000 for very common treatments. Although this denominator strongly influences significance, the magnitude of z does not measure the degree of association; it has no direct interpretation other than statistical significance tests.

A combination of z (or Chi-square) and C, appropriately assesses a particular judgment from a scientific standpoint. If an injury exists, if a medically unacceptable treatment or procedure was used, if the injury is significantly more common statistically with the treatment administered and if the Coefficient of Causality (C) is greater than a specified measure of proof (51,..., 90 percent), then an award should be made under current tort law.

Applying the Model

Current Trial Practice

Although its complexity may make it impractical, the Coefficient of Causality can theoretically clarify the likelihood of proximate cause, even in current trial practice. To illustrate its application, we tried to find data from actual cases. Unfortunately, even the simple data required for the model (and for logical completeness) are usually not available from trial transcripts. In both cases we had to supplement the data with estimates and even use one case where the treatment was clearly acceptable at the time of the incident. Therefore, too much emphasis should not be placed on the illustrations without observing the interpretations and cautions outlined in the text. We will assume that the differences are statistically significant.

CASE A: Prophylactic Use of Gamma Globulin in Blood Transfusion[20]

According to an editorial in the *Journal of the American Medical Association,*[21] routine administion of gamma globulin after blood transfusion should be given serious consideration since it has been reliably demonstrated that: (1) serum hepatitis from blood transfusion causes death in approximately one of every 150 transfusions in persons over 40; (2) the attack rate of hepatitis after transfusion for this age group is 20 percent; (3) in approximately three quarters of the persons over 40 receiving transfusions, gamma globulin has prevented serum hepatitis, and therefore prevented such deaths.

Suppose that a patient died from hepatitis following transfusion without gamma globulin, and suppose that using gamma globulin was the accepted medical practice. The prosecution could establish the terms for the coefficient as follows:

R_1 is *not* administering gamma globulin with the transfusion
R_0 is administering gamma globulin
D_1 is death
D_0 is no death

The probability of hepatitis and death with and without gamma globulin (GG) and the resulting matrix are as follows:

Without GG:

$$(20\%)\left(\frac{1}{150}\right) = (.20)(.0067) = .00134$$

With GG:

$$\left(1-\frac{3}{4}\right)(20\%)\left(\frac{1}{150}\right) = (.25)(.20)(.0067) = .000335$$

	D_1	D_0	*Total*
R_1	.00134 (a)	.99866	1.0
R_0	.000335(b)	.999665	1.0

$$C = \frac{a-b}{a} = \frac{.00134 - .000335}{.00134} = \frac{.001005}{.00134} = .75 = 75\%$$

Therefore, in a large number of patients *not* treated with gamma globulin, 75 percent of the deaths could have been prevented. Whether this represents the "preponderance of the evidence"

or "reasonable medical certainty" in a particular case depends on the measure of proof. The intervening presence (or absence) of hepatitis in this instance reveals the common sense logic implicit in C—if GG prevents 75 percent of hepatitis, then it will prevent 75 percent of the deaths—that is not usually apparent where the intervening mechanism is not as clear.

CASE B: Surgical Intervention in Fracture Dislocation of the Cervical Spine[22]

An accidental fall rendered a young man quadriplegic. The attending surgeons placed him in traction with Crutchfield tongs and the prosecution alleged that they should have operated (laminectomy or anterior decompression). The defense established that it was acceptable practice not to operate at the time of the incident. Let us assume, as an illustration only, that the therapy was inappropriate; the Coefficient of Causality would have demonstrated the low probability of a different outcome. First, we define the terms of the matrix:

R_1 is the alleged negligent treatment, that is, traction
R_0 is the alleged acceptable treatment, that is, surgical procedure
D_1 is quadriplegia, as suffered by the patient
D_0 is a less severe form of paralysis, perhaps even walking

The transcript does not provide specific data on the alleged negligent treatment outcomes, but it was agreed that a very small percentage would improve, perhaps as follows:

	D_1	D_0	*Total*
R_1	.99(a)	.01	1.00
R_0	.96(b)	.04	1.00

$$C = \frac{a - b}{a} = \frac{.99 - .96}{.99} = \frac{.03}{.99} = 3\%$$

The low probability of benefit combined with the operative mortality made traction an acceptable therapy at the time. The coefficient C shows the probability that the paralysis would have been reduced by operation. Thus, given a long series of similar cases, 97 percent would remain as seriously paralyzed, regardless of therapy.

Used in this way, the Coefficient of Causality would at least clarify the proximate cause problem before a measure of proof was applied.

Proportionate Compensation

By introducing probability concepts into the evidentiary standards for proof of proximate cause, we relieve the expert of supplying certainty where none exists. But still another source of uncertainty and unequal distribution of justice exists. By a dichotomous decision of negligent or not negligent, compensation is all or nothing depending on an arbitrary measure of proof.

The Coefficient of Causality may vary from 0 to 100 percent. If the measure of proof is set high, say 90 percent, most patients damaged as a result of improper treatment would obtain no compensation; if it is set low, say 15 percent, many physicians will be found liable whose actions, even though improper, contributed little to the likelihood of injury. If the measure of proof is unspecified, then the current fluctuation from one decision to the next and the lack of a rational basis for many of the awards will continue.

A peculiar property of the Causality Coefficient suggests an alternative—adjusting the awards by the value of C. Assume, in Cases A and B, that negligence and proximate cause were held present, and that the amounts of the awards had each been set (by some formula beyond the scope of this discussion) at $100,000. Adjusting the award for the statistical expectation of damages would give $75,000 equals .75 times $100,000 to Case A, and $3,000 equals .03 times $100,000 to Case B. Several properties make this adjustment more equitable: (1) no arbitrary measure of proof is necessary, (2) no *individual* fault need be assigned and (3) the sum of all awards will equal the sum of the dollar value of all damages due to unacceptable treatment.

With C equaling 50 percent, for example, in a series of 100 injuries, 50 would be attributable to the negligent treatment. At $100,000 per award, total compensation should be 50 times $100,000 equals $5,000,000. Since precise identification of the exact 50 injured has no meaning, proportionate compensation would award in all 100 individuals 50 percent or $50,000. Total expenditures are then equivalent to the total value of the disabilities, that is, 100 times .5 times $100,000 equals $5,000,000. From the individual standpoint, this method is consistent with compensation concepts proposed for other human injury awards.[23]

The plan assures that all plaintiffs with some merit to their claims, recognizing that unacceptable practice was present, would be compensated in proportion to their merit instead of all or nothing. Thus, health care providers through an insurance pool would bear the full cost, but only the cost of the morbidity and mortality attributable to medical injury. Guaranteeing insurance to all

providers who met specified qualifications, pooling all premiums in a single insurance fund and public financing of administrative costs would facilitate operation of the plan. Although this proposal departs significantly from the current system, we believe the concept is worthy of investigation to improve the inadequate, erratic feedback from present tort litigation.

The plan offers other potential efficiencies. If a suitable administrative mechanism were created to investigate cases and make awards, then not only could the concept of individual fault be abolished, but suit could be brought directly against the fund with anonymity granted to the defendant provider. This is in keeping with the probabilistic nature of outcomes, since it is only a matter of chance, even with improper treatment, which physicians' or hospitals' patients suffer a bad outcome. Since the penalty strikes unpredictably, the stigma of negligence serves little purpose in improving the quality of medical care.

On the other hand, the suggested plan would give providers a strong economic impetus to upgrade the quality of health services. Since risk would be spread over the profession and industry as a whole, depletion of the professional liability fund would create a common interest in altering the patterns of care that predisposed to the compensated injuries. With data from the plan, the professions would not be limited to circumstances in individual cases, but could institute a wide variety of feedback responses such as changes in licensing, continuing education, peer review, reimbursement, staffing patterns, administrative procedures and many others.

With adequate funding and staff, review of cases might be done by some specialized branch of the judicial system, like Workmen's Compensation, or perhaps by the Professional Standards Review Organizations currently being established.[24,25] The complexities inherent in the issues, as outlined, defy comprehension by a jury; specialized staff, hearing procedures and records (without some of the courtroom rigidities) are required for rational consideration of the problems.

Such a plan would be superior to arbitration: it would remove the blame or stigma that persists in that adversary proceeding, and it could establish more consistency and fairness in the awards, even without the formulas described above. Most important, the feedback obtained from accumulated cases could improve the quality of medical care, whereas the informal, unrecorded, almost secret deliberations of multiple arbiters gives no systematic understanding for improving health care practices.

Conclusion

The scientific meaning of "proximate cause" means that attributing particular outcomes (good or bad) to particular provider actions is untenable, except in rare instances, and that it serves little social purpose—either in compensating the victims or in deterring the practice of poor medical care. Unless the patient's case is of the type and severity that generates inflated awards, the burdens of proof and the time and expense of a trial preclude rapid, adequate compensation. For the provider, penalties fall erratically so legal liability is not a significant deterrent to poor medical care.

Statistical examination of proximate cause suggests that the no-fault concept of automobile insurance does not apply in the medical setting. Furthermore, most reimbursement from a strict liability or no-fault system such as Workmen's Compensation would necessarily be for the results of disease and injury that were not attributable to the health system in any sense. Unless outcomes are related to standards of care, no firm ground exists for tying compensation to the health system; a public social insurance fund could compensate the disabled more equitably and efficiently.

But social insurance would remove a potentially strong stimulus for regularly upgrading the quality of medical care. Pooling provider premiums in a single fund and making awards systematically according to defined standards could abolish findings of *individual* fault and provide strong economic incentives to improve medical care. This would be a major advantage over ad hoc arbitration which retains the concept of individual fault and provides no feedback for improving health care delivery. Regardless of the merits of the particular suggestions for alternatives made here, many of the current inequities grow directly from a conflict between the probabilistic nature of disease processes and medical judgment, and the all-or-nothing requirement to establish individual fault in the tort system.

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Special Article

Community Mental Health in California

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THE CALIFORNIA COMMUNITY mental health program (under the Lanterman-Petris-Short act) is now five years old. At this half decade mark, it seems appropriate to comment on the impact of the program and to review its prospects and problems.

The Lanterman-Petris-Short act (LPS) had two major goals. The first was to protect the civil rights of the mentally ill by ending indefinite involuntary commitment. The second was to shift patient care from distant state hospitals to local communities and to decrease reliance on inpatient treatment. These goals have been met and national attention has focused on California's approach to treatment of the mentally ill. Many psychiatrists view LPS as the model law to be adopted by other states. Massachusetts, New York, Pennsylvania and others have initiated steps to bring about changes in the care of the mentally ill that are closely patterned after the success of LPS.

These changes in mental health treatment in California have not occurred without concern and criticism. We have witnessed protest over the closure, or threatened closure of state mental hospitals. The roots of this protest are to be found in economics, politics, concern that the mentally ill are neglected and fears about dangerous mental patients in the community.

Economics

Several state hospitals which have been closed were located near small communities. Hospital closure meant the loss of a large payroll. Little planning was done about the impact of these changes on state hospital staff members who lost their jobs and were forced to move away or to find other work in their communities. Those who affiliated with community mental health programs were unable to transfer seniority, retirement and other accrued state benefits.

The California State Employees Association which represents state hospital employees, initiated efforts to prevent further state hospital closures. A historic first was registered when the legislature, for the first time in 27 years overrode a gubernatorial veto on a bill which requires legislative approval before additional state hospitals are closed.

Politics

Political pressure has also been apparent because of the 1974 election. Most of the changes in community mental health in California have occurred during the tenure of a strong, conservative Republican governor. Many opponents of the Administration have labeled the new approach a money-saving device aimed at reducing costs without regard for patients. The closure of state hospitals became a campaign issue rather than a question requiring scientific evaluation. The accomplishments of community programs and the problems in a state-hospital system are better evaluated by professionals than by a political debate. Those who sought to politicize these issues failed to acknowledge that the California mental health legislation was a bipartisan endeavor.

Concerns About Adequacy of Care

In addition to economic and political pressures, there has been public concern about the adequacy of care for mental patients who are treated in the

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community. It is probably the most serious question to be raised. Investigations of community care of chronic patients have revealed great variability among the various county programs. Inadequate housing, lack of professional care and insufficient attention to rehabilitation have been described in some counties.[1] Other local programs have given high priority to the treatment of chronic patients and have devised innovative and effective programs. The controversy centers around whether to reopen state hospitals to provide humane custodial care, or to improve treatment and rehabilitation in the home community. The consensus would seem to be that public care of the mentally ill has improved, and few would choose to go back to the old system of reliance on state hospitals to treat the majority of mentally ill patients.

Danger

Another public concern relates to fears that dangerous mental patients have been released from state hospitals. Several dramatic mass murders have occurred in California since the enactment of LPS and in some instances the alleged murderer was a former state hospital patient. The news media have given wide publicity to these events and have suggested that a need for protecting the public is evident. Those who take this position ignore the fact that the ex-patients were adjudged sane at the time of their release and therefore could not be detained legally under any system. Second, the overwhelming majority of murders are committed by people who were never in psychiatric treatment or in state hospitals. All studies reported to date, indicate that former mental patients are less likely or no more likely to be arrested for crimes of violence than the average citizen.[2-6] In a study of former state hospital patients in New York State, the arrest rate of a group of 5,833 patients was 6.9 per thousand. This compared with an arrest rate of 99.7 per thousand in the general adult population during that same year. In another study of 1,000 patients who had formerly been at Middletown State Hospital in New York, the average annual arrest rate among this group was 2.4 per thousand. This group was followed for 10 years. In another study of 741 patients from other New York State Hospitals, the annual arrest rate among men was seven per thousand and among women was one per thousand. This group also was followed over a 10-year period. In a report by Rappaport and Lassen, the arrest rate among men who had been state hospital patients was similar to that in the general population except for the offense of robbery. Murder, manslaughter, rape and aggravated assault were offenses committed by former mental patients less frequently or at the same rate as in the general public. In a study of women, reported a year later, those who had a history of mental illness had an arrest rate for murder, robbery and manslaughter which was less than or the same as the rate in the general population. There was a somewhat higher arrest rate in this group for aggravated assault.

Ekblom, in a book published in 1970,[2] states that in Sweden, the risk of injury from mental patients was less than the risk of injury from employment in a factory or other industrial situation. Macdonald made a study of 100 patients who had made homicidal threats. Twenty-one months later (when all of the patients had been released) there had been only one person of that group of 100 who had actually committed murder. The idea of incarcerating 99 to keep one from homicide is a high price. The fact is that psychiatrists have great difficulty in predicting dangerous behavior. The only satisfactory predictor of violent behavior is a history of repeated violent acts. The law already provides for involuntary detention of a person who presents a clear threat to others. The roots of criminal behavior are to be found in social conditions of poverty, ghetto life and powerlessness. Psychiatric treatment does not prevent crime or cure its major causes.

Community Treatment Versus State Hospitals

The debate about whether community treatment or state hospital treatment is more effective is not easily settled. Matters of treatment philosophy, economics, public attitudes and politics all enter into the discussion. It is unlikely that one system or the other can manage all of the problems of mental illness. It is more likely that a balanced system of care is needed in which state hospitals and community treatment programs each have some role. As the law is currently structured, all admissions to state hospitals must be authorized by the County Mental Health Director. The need for state hospitals is clearly related to the number of admissions from each county. The reduction of referrals for admission has brought about the declining census in state hospitals rather than any wholesale discharge of resident patients. These rates of admission to state hospitals have varied greatly from county to county although the net

effect statewide has been a significant reduction in rates of admission to state hospitals.

Table 1 shows the admission rates to state hospitals from the medium and large (in population) California counties over the past five years. These data are derived from a report of the California Department of Health. The data reports *rates per hundred thousand population,* and not raw numbers of admissions. During 1973-74, the estimated rate ranged from 0 (Fresno) to 175 (Los Angeles). In the preceding year (1972-73) the rate ranged from two (Santa Barbara) to 240 (Alameda). It should be noted that all counties except Los Angeles and Orange show a significant reduction over the five-year period. The entire state shows a 39.5 percent reduction in state hospital admission rates over the same five year period.

It is reasonable to ask why there is such variation in reduction of state hospital admission rates. The major factor is the ability of the community program to provide a full range of treatment programs. Urban versus rural settings may also be a factor reflecting differences in the type and extent of mental disorder. The state of development of the community program is another factor since there were some community mental health programs which were well-established when LPS was enacted, and others were just beginning at that time. Finally, the preference of the local community and the program director may be the most important determinants of admission rates to state hospitals.

The relationship of change in state hospital admission rates to the development of community programs is shown in Table 2. This table compares the change in state hospital admission rates with changes in services rendered by community programs. Total community services (outpatient, inpatient and partial day in hospital services) are presented along with figures for change in outpatient services only. Data are presented for the years 1969-70 and 1972-73. These data are chosen because they are the most recent data from the Department of Health. If one were to go back farther or to have data for 1973-74, the picture might be somewhat different in magnitude, but would probably show the same direction. The change for Sacramento County is shown as a reduction of 95 percent in state hospital admissions and an increase of 176.6 percent in outpatient visits in the community mental health program. If we were to compare the years 1967-68 with 1973-74, it would show a reduction of state hospital admissions of 98.6 percent and an increase in outpatient visits of approximately 1,614.3 percent. However, data for all counties are not available for those years and for this reason we restrict ourselves to the 1969-70 and 1972-73 years.

In most of the counties a major reduction in admissions to state hospitals is accompanied by an increase in local treatment programs. In Contra Costa County there is a large decrease in state hospital admissions but a small decrease in community services (especially outpatient visits). Actually there was an increase in outpatient visits in Contra Costa County between 1969-70 and 1970-71, but then a decline in 1971-72 and 1972-73. The latter may reflect local preferences, special problems in the community program or simply a lack of available community mental health serv-

TABLE 1.—*Admissions to State Hospitals in Heavily Populated California Counties (Rate per 100,000)*

County	*Population* (1970)	1969-70	1970-71	1971-72	1972-73	1973-74*
Alameda	1,073,184	305	433	246	240	172
Contra Costa	555,805	330	297	102	40	27
Fresno	413,329	32	45	20	2	0
Los Angeles	7,036,987	139	187	183	187	175
Marin	206,758	207	348	65	41	39
Orange	1,420,248	119	203	157	157	141
Riverside	459,074	185	217	189	155	131
Sacramento	634,190	60	44	23	3	2
San Bernardino	681,535	299	193	66	101	103
San Diego	1,357,854	45	46	39	12	3
San Francisco	715,674	598	218	122	108	92
San Mateo	556,601	245	210	112	40	36
Santa Barbara	264,324	44	19	3	2	6
Santa Clara	1,066,421	250	229	87	22	16
Total State	19,953,134	185	198	146	129	112

*Estimate.

ices. In Orange County there has been a large increase in community mental health services, especially in outpatient visits. At the same time there has been an increase in state hospital admissions. This probably reflects the fact that Orange County started its community program somewhat later than some of the medium and large size counties. In the early stages of any community program there may be an increase in the use of hospital services (locally or in state hospitals) while alternatives to admitting patients to hospital are developed. Although Orange County increased its admission rate during the years cited, it reduced its state hospital inpatient days by 27.1 percent reflecting diminished use of state hospitals for long-term treatment. Los Angeles also shows increased admission rates, but a decrease in number of state hospital inpatient days (also reflecting the fact that Los Angeles County uses a local state hospital for acute inpatient treatment).

The statewide trends point to a reduction of state hospital admissions and use of state hospital inpatient days throughout the system. Concomitantly there is generally an increase in community mental health services, especially in outpatient visits. We suggest that the largest decrease in state hospital utilization has been in those counties which have shown the largest increase in community services, especially in those counties that have developed community services for the chronically mentally ill—former state hospital patients. Perhaps the point might be more poignantly illustrated by a case example—the changes that have taken place in Sacramento County. We will pay special attention to programs of aftercare (or continuing community care) of the chronically mentally ill.

Before 1968, Sacramento County had a two-tiered system of mental health care which encouraged reliance on the state hospital system for long-term care and the State Bureau of Social Work for aftercare services. Community treatment was relatively unavailable. In 1968, with the leadership of the new School of Medicine at the University of California, Davis, and the mandate of LPS, a community mental health program began. As local treatment services expanded, state hospital admissions declined significantly. Chart 1 shows the decrease in admissions to state hospitals during the period 1968-73 through 1973-74. This reduction of state hospital admissions was made possible by a pronounced increase in local treatment programs. Outpatient services were approximately 7,000 visits in 1967-68 and approximately 120,000 for 1973-74 (the estimates made when the chart was drawn have been exceeded). Equally important has been the diversification of community mental health services to include day in hospital, crisis intervention, aftercare enrichment and specialized programs for children, families, drug and alcohol abusers and other categories of people needing help.

The special challenge has been former state hospital patients. In some communities in Cali-

TABLE 2.—*Changes in State Hospital Services and in Community Mental Health Services 1969-70 to 1972-73*

	State Hospital Admissions (Percent)	*State Hospital Inpatient Days (Percent)*	*Community Mental Health Services* (Percent)*	*Change in Outpatient Visits Only (Percent)*
Alameda	−21.2	−45.1	+ 4.6	+ 2.3
Contra Costa	−88.0	−54.5	− 3.8	− 10.6
Fresno	−94.8	−97.5	+118.0	+143.7
Los Angeles	+33.9	−30.9	+ 12.2	+ 30.6
Marin	−80.4	−60.2	+ 57.3	+ 40.5
Orange	+32.0	−27.1	+ 83.0	+173.2
Riverside	−15.8	−19.4	+977.0	+793.8
Sacramento	−95.0	−82.8	+ 95.6	+176.6
San Bernardino	−66.1	−62.4	+439.2	+782.9
San Diego	−74.0	−63.5	+ 29.6	+ 57.8
San Francisco	−81.9	−64.4	+ 40.0	+ 43.1
San Mateo	−83.8	−54.5	+ 51.5	+ 29.9
Santa Barbara	−95.7	−82.4	+120.8	+197.4
Santa Clara	−91.1	−70.4	+109.6	+122.2
Total State	−30.0	−52.2	+ 55.3	+ 79.9

*Includes outpatient visits, inpatient days, partial hospital days and residential treatment days.

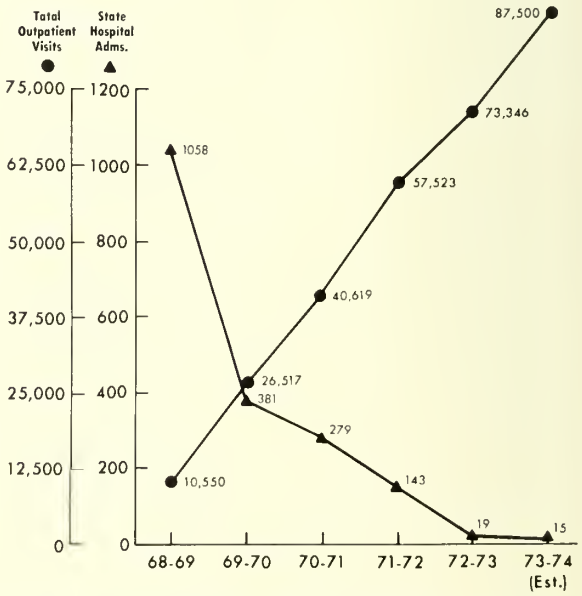

Chart 1.—Admissions to state hospitals and community mental health outpatient visits in Sacramento county.

fornia there has been inadequate attention to this group. They have generally been excluded by families because of long periods spent in hospitals. They are frequently housed in board-and-care homes which may provide food, clothing and shelter, but lack the resources to offer rehabilitation and treatment. Those with chronic illness frequently come to the attention of police, who feel frustrated by an inability to deal effectively with their problems. In such cases the patient may be returned to the state hospital, or kept in the community without adequate treatment.

Sacramento County planned special programs for those with chronic mental illness. In a series of services called Community Alternatives to State Hospitalization (the acronym CASH was created to emphasize the need for funding), the Sacramento program included:

- Comprehensive mental health services in each catchment area (thus identifying the agency responsible for all of the mentally ill).
- Crisis responsiveness including mobile crisis intervention.
- Patient follow-up care system.
- Rehabilitation-resocialization programs.
- Intermediate care facilities.
- Volunteer programs.
- Information-education programs.

The first requirement of a program for treatment of the chronically ill involves a commitment and responsibility to the total population. Sacramento County has a mental health team (50 to 80 staff members) for each of its five catchment areas—each team committed to meet the total mental health needs of its entire catchment area. That system identifies the professional group responsible for treatment of acute and chronic illness in adults and children and for prevention and early identification of illness. Patients who have been treated in a state hospital are discharged after treatment planning with the catchment area team. That team also works closely with a group of professional social workers in the Community Services Section (CSS) of the State Department of Health. These social workers are involved in visting board-and-care homes and families in order to provide continued care and follow-up treatment. Patients, families and board-and-care home operators are all in contact with the catchment area team and the CSS worker.

Crisis intervention has been the priority of the Sacramento County program. Crisis responsiveness means that patients, family members and board-and-care home operators can obtain immediate help from a 24-hour crisis intervention team staffed by mental health professionals. Where appropriate, members of the mobile crisis team will travel to the patient. The catchment area teams provide regular contact with residential-care home operators including consultative visits and mutual treatment planning. Patients are transported to special aftercare clinics operated by the catchment area teams. They are maintained on medication where appropriate. The aftercare program includes individual and group psychotherapy and the availability of any appropriate mental health treatment. When indicated, intensive inpatient, partial day in hospital and outpatient treatment is available.

The patient follow-up care system includes accurate clinical records of all phases of treatment. It allows a mental health team to contact those patients who do not keep appointments. Close contact with the public guardian (the conservator of some patients) and the availability of inpatient crisis treatment with a minimum of red tape insures that such patients can be helped through critical situations promptly.

A rehabilitation-resocialization program operated under contract by the Community Services Section is aimed at rehabilitation of former state hospital patients. Such patients are either transported or taught to take the bus from a board-and-care home to a daytime treatment program. The rehabilitation staff includes social workers, recreational therapists, paraprofessionals and mental health volunteers from the catchment area Volunteer Unit. Three such resocialization-rehabilitation centers work closely with the catchment area teams. Patients are not permitted to sit in front of a television set day after day.

Intermediate levels of 24-hour care have been developed to offer more professional staff and direct treatment than is possible in a board-and-care home. This type of facility is useful for patients who do not require the most intensive (and costly) hospital services, but who require active inpatient treatment. Special contracts have been developed with two "L" facilities which augment the available staff with mental health professionals. This type of intermediate facility allows greater flexibility and community treatment of patients who might otherwise be readmitted to a state hospital.

The use of mental health volunteers is exten-

sive. There is a volunteer program in each of the five catchment areas. Each Volunteer Unit has a half time salaried staff coordinator provided by the Sacramento Area Mental Health Association (under a contract with the County Mental Health Service). The Mental Health Association and staff coordinators recruit and train volunteers, and operate a program which is closely coordinated with the catchment area team. Volunteers make visits to board-and-care homes, participate in the rehabilitation centers and are active in treatment programs at each of the five catchment area mental health centers.

Finally, information-education has a high priority. Public information is a major focus with efforts being directed through the media and personal presentations in service organizations and educational groups. The education of human service professionals and of laypersons are equally important. Special attention is paid to primary care physicians, ministers, probation officers and social agencies of all types. The education program has communicated information about program and resources (as well as results) to the general public and to health professionals.

The Sacramento experience has convinced us that a comprehensive community program can treat chronic patients, as well as those with acute illness. It is this former group which is most likely to require readmission to state hospitals, or to suffer from lack of treatment without special attention. We are aware that the Fresno and Santa Barbara County programs have also developed specialized programs for former state hospital patients. These three county programs are those which have had the largest decrease in state hospital inpatient days and the largest increases in outpatient visits among the community programs. A combination of community mental health programs and special attention to the needs of the chronically ill demonstrate that community programs can minimize the use of state hospitals and still provide quality care to all patients.

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Refer to: Craven PC, Morrelli HF: Chelation therapy (Medical Information). West J Med 122:277-278, Mar 1975

Medical Information

Chelation Therapy

PHILIP C. CRAVEN, MD
HOWARD F. MORRELLI, MD
San Francisco

This statement was prepared in response to a request made to the Clinical Pharmacology Service at the University of California, San Francisco to evaluate the potential therapeutic uses and the possible toxicities of chelation therapy. The question arose in regard to the use of ethylene tetraacetic acid (EDTA) in the treatment of atherosclerotic cardiovascular disease.

Action

Disodium edatate (Na_2 EDTA or edathamil or versenate) is a complex molecule whose only recognized pharmacologic action is the chelation of certain divalent and trivalent cations (such as calcium, zinc, cadmium, mangnanese, lead, vanadium and plutonium). Following oral administration, 80 to 95 percent of the dose appears in the feces within 24 hours. After intravenous administration, 95 percent of the dose appears in the urine by 24 hours and less than 0.5 percent remains in the body after 48 hours. The compound is not metabolized and is handled by the kidneys as inulin is, so that alterations in urine flow rate and pH do not affect overall excretion rate of EDTA, although impaired renal function with reduced glomerular filtration will delay excretion.[1]

Disodium-EDTA administered parenterally binds serum calcium very rapidly, and administration rates greater than 15 mg per minute produce hypocalcemic tetany. Slower rates do not affect serum calcium levels, but mobilize bone calcium and induce hypercalcuria. (Calcium-Na_2 EDTA does not affect plasma or body levels of calcium, but otherwise has the same actions and toxicities as the unchelated form).[1]

Accepted Therapeutic Uses and Doses

The single, generally recognized use of EDTA is in the diagnosis and treatment of lead poisoning.[1-4] Other reported and suggested uses are in the diagnosis of hypoparathyroidism, the treatment of porphyria, scleroderma, hypercholesterolemia, hypercalcemia, calcific cardiac valvular disease, cardiac arrhythmias and atherosclerotic coronary artery and peripheral vascular disease.[1,2] Most of these uses are considered "investigational."[2]

Recommended chelation therapy in acute lead intoxication includes the combined parenteral administration of 2,3 dimercaptopropanol (BAL) and Ca EDTA, the latter in doses of 50 to 75 mg per kg of body weight per day for five days, followed by long-term oral therapy with D-penicillamine.[5] The dose of Ca EDTA should exceed 50 mg per kg of body weight per day only when combined with BAL, and even using the recommended dosage schedule, the following side effects have been observed: fever, hypercalcemia, proteinuria, microscopic hematuria and large epithelial cells in the urinary sediment. Therefore, frequent urinalyses and determination of serum electrolytes, blood urea nitrogen, calcium, phosphate and alkaline phosphatase are recommended during therapy.[5] Long-term therapy is considered unwarranted because of potential renal toxicity.[6]

Toxicity

Fatal and nonfatal renal toxicity in humans given large doses of EDTA has been well documented. Reported symptoms include nocturia, frequency and urgency of urination and dysuria. Results of urinalyses have shown albumin, parenchymal cells, granular casts and red and white blood cells. In two fatal cases reported, severe renal tubular damage and widespread engorgement of reticuloendothelial cells were noted at autopsy.[7,8]

Well-designed experimental studies using rats showed that Ca EDTA caused severe hydropic degeneration of proximal tubules, with casts and epithelial cells in urine, that was clearly dose dependant.[7] Other tissues were not affected. The ED-50 (the dose required to produce the first histologic evidence of damage in 50 percent of

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animals treated daily for 16 days) was 203 mg per kg of body weight per day. Lesions developed in none of the animals given 62.5 mg per kg of body weight per day for 16 days. Neither acidification nor alkalinization of the urine affected the development of lesions.[7] These studies form the major basis for the dose recommendations in man: not more than 5 grams (70 mg per kg of body weight) per day for not more than five days, followed by a two-day rest period.

Other toxicities reported include thrombophlebitis (probably related to concentration of the solution); hypocalcemia after rapid administration of disodium EDTA; systemic symptoms of malaise, fatigue, thirst, fever, then myalgia and headache in a characteristic sequence often heralding renal toxicity; histamine-like reactions; glycosuria without a diabetic state; anemia in one case; dermatitis similar to that seen with avitaminosis B, especially B_6;[9,10] and fatal emboli in a patient with calcium deposits in heart valves.[11] Congenital malformations and fetal deaths were consistently observed after administration of EDTA to pregnant rats; these changes were prevented by administration of zinc.[12]

Use in Atherosclerotic Cardiovascular Diseases

In 1955, a case report regarding EDTA therapy in a patient with severe nephrocalcinosis states, on the basis of serial x-ray films of the abdomen, that there was a 50 to 65 percent decrease in renal metastatic calcium following prolonged therapy with intravenously given EDTA totalling 575 grams in 13 months; neither renal function, nor side effects were reported.[13]

The same authors reported dissolution of mitral valve calcification and relief of congestive pulmonary symptoms following EDTA therapy in a patient with rheumatic heart disease, and removal of metastatic calcium from a necrotic sinus tract in a patient previously operated on for thyroid malignancy.[11] Extrapolating from these experiences, the authors reported treating 20 patients with progressive angina pectoris with prolonged courses of EDTA (5 grams daily for five days, followed by a two-day rest period, to a total of 75 to 300 grams).[11] Results were reported in terms of subjective symptomatic improvement. Also of 17 patients with abnormal findings on electrocardiograms, six were stated to have improved; and electrocardiograms from two patients were displayed, but the improvements were difficult to interpret. One patient died following a convulsion; results of autopsy showed extensive aortic atheromatosis and it was suspected "that he died from a calcium embolus that had been freed from a large arterial plaque." No other toxicities were apparently monitored nor commented upon.[11]

Results of a third study, involving ten men with disabling angina pectoris, were also reported in terms of subjective symptomatic improvement and changes noted on electrocardiograms, without mention of toxicities.[14] No well designed, controlled studies with blindly read, objective results have been reported.

Because of the risk of severe renal toxicity, and the lack of objective evidence suggesting therapeutic benefit from EDTA therapy for atherosclerotic disease, such therapy should be regarded as investigational and conducted under carefully controlled conditions in an academic institution by experienced investigators.

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in memoriam

Benioff, Mortimer Alexander, San Francisco. Died October 12, 1974, aged 62. Graduate of the University of California Medical School, Berkeley-San Francisco, 1938. Licensed in California in 1938. Dr. Benioff was a member of the San Francisco Medical Society.

Cole, Edwin Revere, Sacramento. Died January 17, 1975 in Yuma, Arizona, aged 70. Graduate of the University of California Medical School, Berkeley-San Francisco, 1931. Licensed in California in 1931. Dr. Cole was a retired member of the Sacramento County Medical Association.

Dostal, Robert J., Santa Monica. Died January 12, 1975 in Los Angeles, aged 75. Graduate of the University of Iowa College of Medicine, Iowa City, 1924. Licensed in California in 1926. Dr. Dostal was a member of the Los Angeles County Medical Association.

Ems, Frederick E., Petaluma. Died January 13, 1975 in Petaluma of heart disease, aged 91. Graduate of Medizinische Fakultät der Ludwig-Maximiliams-Universität, Munich, 1908. Licensed in California in 1940. Dr. Ems was a retired member of the Sacramento Medical Association.

Furze, William E., Fresno. Died January 15, 1975 in Fresno, aged 63. Graduate of the Creighton University School of Medicine, Omaha, 1938. Licensed in California in 1939. Dr. Furze was a member of the Fresno County Medical Society.

Golden, Ross, Laguna Hills. Died January 10, 1975 in Santa Ana, aged 85. Graduate of Harvard Medical School, Boston, 1916. Licensed in California in 1952. Dr. Golden was a retired member of the Los Angeles County Medical Association.

Hansen, Fred M., Santa Ana. Died January 4, 1975, aged 60. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1941. Licensed in California in 1941. Dr. Hansen was a member of the Orange County Medical Association.

Henderson, George A., Ontario. Died January 5, 1975 in Ontario, aged 64. Graduate of Kansas City College of Osteopathy and Surgery, Kansas City, MO, 1958. Licensed in California in 1959. M.D. degree from California College of Medicine, 1962. Dr. Henderson was a member of the San Bernardino County Medical Society.

Ortega, Leonard F., Oakland. Died February 1, 1975 in Kentfield of carcinoma of the colon, aged 57. Graduate of St. Louis University School of Medicine, 1943. Licensed in California in 1947. Dr. Ortega was a member of the Alameda-Contra Costa Medical Association.

Prindle, Kirk Hubbard, San Mateo. Died December 29, 1974 in San Mateo, aged 77. Graduate of the University of Oregon Medical School, Portland, 1924. Licensed in California in 1928. Dr. Prindle was a retired member of the San Mateo County Medical Society.

Richards, William Wilson, San Francisco. Died January 8, 1975, aged 59. Graduate of the University of California Medical School, Berkeley-San Francisco, 1938. Licensed in California in 1938. Dr. Richards was an associate member of the San Francisco Medical Society.

Stotler, Robert Cresap, Carlsbad. Died August 10, 1974 of asphyxiation due to obstruction in larynx (meat bolus), aged 54. Graduate of the George Washington University School of Medicine, Washington, D.C., 1947. Licensed in California in 1953. Dr. Stotler was a member of the San Diego County Medical Society.

Thormann, Jerome Arthur, Fresno. Died January 29, 1975 in Fresno, aged 66. Graduate of State University of Iowa College of Medicine, Iowa City, 1934. Licensed in California in 1936. Dr. Thormann was a retired member of the Fresno County Medical Society.

Wells, Carl D., Berkeley. Died January 4, 1975 in Oakland of heart disease, aged 48. Graduate of the University of California School of Medicine, Berkeley-San Francisco, 1953. Licensed in California in 1954. Dr. Wells was an associate member of the Alameda-Contra Costa Medical Association.

Wolf, George Glenn, Fresno. Died January 25, 1975 while clamming in the surf near Pismo Beach, aged 55. Graduate of Washington University School of Medicine, St. Louis, 1947. Licensed in California in 1947. Dr. Wolf was a member of the Fresno County Medical Society.

BOOK REVIEWS

THE WESTERN JOURNAL OF MEDICINE does not review all books sent to it by the publishers. A list of new books received is carried in the Advertising Section.

HAZY .? CRAZY .? AND/OR LAZY .?—The Maligning of Children with Learning Disabilities—Joseph H. Rosenthal, MD, Director, Learning Disabilities Clinic, Department of Pediatrics, Kaiser-Permanente Medical Clinic, Oakland. Academic Therapy Publications, 1539 Fourth Street, San Rafael (94901), 1973. 210 pages, $3.75.

A good physician must learn what he knows and what he doesn't know, what he is and what he is not. Having determined that he is a pediatrician, not a psychiatrist or a school teacher or counselor or a psychologist or a psychometrist, the physician should find Dr. Rosenthal's book of great value and support. It presents an individualized approach that takes advantage of an encyclopedic familiarity with the literature.

There is a good review of the assorted categories and diagnoses used, recognizing their limited meaning. Dr. Rosenthal recognizes that children come with parents and with schools, and none are "all o.k." or "all not o.k." He also accepts the expectations that middle-class America has of its schools and its children . . . a lot!

Perhaps one of the most useful concepts is the thesis that there are children who are inherently "different" (organic), and that many school, social and family problems are secondary and/or interrelated. Many mothers need help and rest, not more guilt or psychiatric counseling. The book is practical, offering management help by examples, as well as through more comprehensive diagnosis.

It is a good book, contains an immense amount of information in a small package, and is the intensely personal experience of a particular kind of well-trained and patient care oriented pediatrician. In a new field, where none of us is always sure of his ground, the well-trained pediatrician who wants to help more of the children in his practice will find Dr. Rosenthal's experiences interesting, useful and entertaining.

HENRY RICHANBACH, MD

* * *

THE PHYSIOLOGICAL AND CELLULAR BASIS OF METABOLIC BONE DISEASE—Howard Rasmussen, MD, PhD, Benjamin Rush Professor of Biochemistry, University of Pennsylvania School of Medicine and Senior Physician, Children's Hospital of Philadelphia; and Philippe Bordier, MD, PhD, Maitre de Recherche-INSERM, Unité de Recherche "André LICHTWITZ" Hopital Lariboisière and Rhumatologue Attaché à la Clinique Rhumatologique de l'Hopital Lariboisière (Pr. De Seze), Université Paris Nord, Paris. The Williams & Wilkins Company, 428 E. Preston St., Baltimore (21202), 1974. 364 pages, $21.50.

This clearly written, beautifully illustrated and well-edited volume presents an attractive and interesting new approach to the understanding of skeletal physiology and pathophysiology. The authors' views are derived from imaginative interpretation of specially prepared bone biopsy specimens, mostly human and some from well-chosen animal experiments. They also review pertinent biochemistry, including recent information about vitamin D metabolism but not the heterogeneity of the parathyroid hormones.

The cellular basis of bone physiology used to be simple: osteoblasts built bone and osteoclasts destroyed it. Each was assumed to arise from a separate cell line. Then in 1963 Bélanger established the rôle of osteocytes in osteolysis, the principal process responsible for maintenance of blood calcium levels.

In this work, Rasmussen and Bordier present new evidence that osteoprogenitor cells (mesenchymal cells, osteocytes, resting osteoblasts) differentiate to become osteoclasts which in turn become osteoblasts together forming bone remodeling units that control resorption and formation. In this theory, bone formation must be preceded by bone resorption. These two processes are necessarily balanced, though how they are linked has been obscure. Imbalanced cellular differentiation changes bone mass and/or calcium balance. Hormones and ions act by shifting the cellular balance. Calcitonin is thought to stimulate transformation of osteoclasts to osteoblasts so that bone resorption is inhibited. But bone formation is not increased because calcitonin also blocks activation of new osteoprogenitor cells. In this schema, corticoids cause osteoporosis: (1) by blocking the transformation of osteoclasts to osteoblasts, (2) by inhibiting the synthesis of bone matrix and, (3) in the presence of the parathyroids, activating osteoprogenitor cells to form osteoclasts. The authors believe that corticoid osteoporosis is mediated by secondary hyperparathyroidism, a mechanism originally suggested by Laron in 1957 and subsequently supported by Eliel (1965), Gordan (1966), Jee (1972) and recently shown directly by Williams (1973). However, in my experience, corticoids first increase accretion and lower the serum calcium level which probably accounts for secondary hyperparathyroidism.

In postmenopausal osteoporosis, insufficient transformation of osteoclasts to osteoblasts is postulated to explain the decline in active bone formation. This concept is in harmony with the classic theory of Fuller Albright and with the kinetic data of Eisenberg and Gordan (1961), Hioco et al (1964) and Lafferty et al (1964), but not with Heaney, Fraser and many others whose data have been interpreted to show normal accretion and increased osteolysis. Rasmussen and Bordier imply from their version of the Albright theory that calcitonin, fluoride and phosphonate cannot be effective therapeutic agents for treating postmenopausal osteoporosis. Similarly, calcitonin can be beneficial in Paget's disease (viewed here as neoplasia of bone remodeling units) only if it does not induce secondary hyperparathyroidism, which, unfortunately, it does.

The authors' theories are stimulating, appear to be well documented and provide a cellular basis for many well-established clinical phenomena. It is refreshing that the focus has been placed on cells in these days when classical bone pathology can hardly be said to flourish. The theory adapts well to many still unexplained and apparently paradoxical phenomena, that is, the beneficial value of corticoids and of cytotoxic chemotherapeutic agents in many hypercalcemias. The publishers have done an outstanding job. The price has been kept reasonable, in large part by reproducing 51 color microphotos in a single transparency which hopefully will not be separated from the volume. Most physicians will find the book highly specialized and theoretical, certainly too much so for most medical students. It is not a textbook of practical diagnosis and treatment. It should prove provocative and useful for workers in the rapidly burgeoning field of investigation on bones, parathormones and vitamin D-derived hormones.

GILBERT S. GORDAN, MD, PH D

Must vasodilators and therapy for other diseases come into conflict?

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the compatible vasodilator... no treatment conflicts reported

The cerebral or peripheral vascular disease patient often has coexisting disease[1] which calls for another drug along with his vasodilator. It may be a hypoglycemic, miotic, antihypertensive, diuretic, anticoagulant, corticosteroid, or coronary vasodilator.

Vasodilan is not incompatible with any of these drugs—no treatment conflict has been reported. And, unlike other vasodilators, Vasodilan has not been reported to affect carbohydrate metabolism, liver function, or intraocular pressure—or to complicate treatment of diabetes, hypertension, peptic ulcer, glaucoma, or liver disease.

In fact, there are no known contraindications to the use of Vasodilan in recommended oral doses, other than that it should not be given in the presence of frank arterial bleeding or immediately postpartum.

1. Gertler, M. M., et al.: Geriatrics *25*:134-148 (May) 1970.

Indications: Based on a review of this drug by the National Academy of Sciences-National Research Council and/or other information, the FDA has classified the indications as follows:

Possibly Effective:

1. For the relief of symptoms associated with cerebral vascular insufficiency.
2. In peripheral vascular disease of arteriosclerosis obliterans, thromboangiitis obliterans (Buerger's Disease) and Raynaud's disease.
3. Threatened abortion.

Final classification of the less-than-effective indications requires further investigation.

Composition: Vasodilan tablets, isoxsuprine HCl, 10 mg. and 20 mg.

Dosage and Administration: 10 to 20 mg. three or four times daily.

Contraindications and Cautions: There are no known contraindications to oral use when administered in recommended doses. Should not be given immediately postpartum or in the presence of arterial bleeding.

Adverse Reactions: On rare occasions, oral administration of the drug has been associated in time with the occurrence of severe rash. When rash appears, the drug should be discontinued. Occasional overdosage effects such as transient palpitation or dizziness are usually controlled by reducing the dose.

Supplied: Tablets, 10 mg.—bottles of 100, 1000, 5000 and Unit Dose; 20 mg.—bottles of 100, 500 and Unit Dose.

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IN GONORRHEA

INJECTION

Wycillin®

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Gonorrhea, according to the national Center for Disease Control, is, if the parenteral route is chosen, most effectively treated with aqueous procaine penicillin G. In uncomplicated cases, administration of 4.8 million units together with 1 gram oral probenecid, given at least 30 minutes prior to injection, is recommended.

Indications: In treatment of moderately severe infections due to penicillin G-sensitive microorganisms sensitive to the low and persistent serum levels common to this particular dosage form. Therapy should be guided by bacteriological studies (including sensitivity tests) and by clinical response.

NOTE: When high sustained serum levels are required use aqueous penicillin G, IM or IV.

The following infection will usually respond to adequate dosages of intramuscular procaine penicillin G.—*N. gonorrhoeae:* acute and chronic (without bacteremia).

For deep intramuscular injection only.

Contraindications: Previous hypersensitivity reaction to any penicillin.

Warnings: Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy.

Serious anaphylactoid reactions require immediate emergency treatment with epinephrine. Oxygen and intravenous corticosteroids should also be administered as indicated.

Although anaphylaxis is more frequent following parenteral therapy it has occurred in patients on oral penicillins. These reactions are more apt to occur in individuals with a history of sensitivity to multiple allergens.

There have been well documented reports of individuals with a history of penicillin hypersensitivity reactions who have experienced severe hypersensitivity reactions when treated with a cephalosporin. Before therapy with a penicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, and other allergens. If an allergic reaction occurs, the drug should be discontinued and the patient treated with the usual agents e.g., pressor amines, antihistamines and corticosteroids.

Precautions: Use cautiously in individuals with histories of significant allergies and/or asthma.

Carefully avoid intravenous or intraarterial use, or injection into or near major peripheral nerves or blood vessels, since such injections may produce neurovascular damage.

A small percentage of patients are sensitive to procaine. If there is a history of sensitivity, make the usual test: Inject intradermally 0.1 cc. of a 1 to 2 percent procaine solution. Development of an erythema, wheal, flare or eruption indicates procaine sensitivity. Sensitivity should be treated by the usual methods, including barbiturates, and procaine penicillin preparatic should not be used. Antihistaminics appear beneficial in tre ment of procaine reaction.

The use of antibiotics may result in overgrowth of nons ceptible organisms. Constant observation of the patient is ess tial. If new infections due to bacteria or fungi appear dur therapy, discontinue penicillin and take appropriate measure

If allergic reaction occurs, withdraw penicillin unless, in t opinion of the physician, the condition being treated is threatening and amenable only to penicillin therapy.

When treating gonococcal infections with suspected prim or secondary syphilis, perform proper diagnostic procedur including darkfield examinations. In all cases in which concoi tant syphilis is suspected, perform monthly serological tests for least four months.

Adverse Reactions: (Penicillin has significant index of s sitization) skin rashes, ranging from maculopapular eruptions exfoliative dermatitis; urticaria; serum sickness-like reactio including chills, fever, edema, arthralgia and prostration. Sev and often fatal anaphylaxis has been reported. (See "Warnings

As with other antisyphilitics, Jarisch-Herxheimer reaction been reported.

Administration and Dosage: Administer only by *deep in muscular injection,* in upper outer quadrant of buttock. In infa and small children, midlateral aspect of thigh may be preferal When doses are repeated, vary injection site. Before injecti aspirate to be sure needle bevel is not in blood vessel. If blo appears, remove needle and inject in another site.

Although some isolates of *Neisseria gonorrhoeae* have creased susceptibility to penicillin, this resistance is relative, absolute, and penicillin in large doses remains the drug of choi Physicians are cautioned not to use less than recommenc doses.

Gonorrheal infections (uncomplicated)—Men or Women: million units intramuscularly divided into at least two doses a injected at different sites at one visit, together with 1 gram of c probenecid, preferably given at least 30 minutes prior to injectic

NOTE: Treatment of severe complications of gonorrhea sho be individualized using large amounts of short-acting penicil Gonorrheal endocarditis should be treated intensively w aqueous penicillin G. Prophylactic or epidemiologic treatment gonorrhea (male and female) is accomplished with same tre ment schedules as for uncomplicated gonorrhea.

Retreatment: The National Center for Disease Control, Ve real Disease Branch, U.S. Dept. H.E.W. recommends:

Test cure procedures at approximately 7-14 days after thera In the male, a gram-stained smear is adequate if positive; oth wise, a culture specimen should be obtained from the ante urethra. In the female, culture specimens should be obtain from both the endocervical and anal canal sites.

Retreatment in males is indicated if urethral discharge persi 3 or more days following initial therapy and smear or cultr remains positive. Follow-up treatment consists of 4.8 million ur I.M. divided in 2 injection sites at single visit.

In uncomplicated gonorrhea in the female, retreatment indicated if follow-up cervical or rectal cultures remain positive *N. gonorrhoeae.* Follow-up treatment consists of 4.8 million ur daily on 2 successive days.

Syphilis: all gonorrhea patients should have a serologic test syphilis at the time of diagnosis. Patients with gonorrhea w also have syphilis should be given additional treatment app priate to the stage of syphilis.

Composition: Each disposable syringe 2,400,000 units (4 size) contains procaine penicillin G in a stabilized aqueous s pension with sodium citrate buffer, and as w/v approximately 0. lecithin, 0.5% carboxymethylcellulose, 0.5% povidone, 0.1% metl paraben, and 0.01% propylparaben. The multiple-dose 10-cc. contains per cc. 300,000 units procaine penicillin G in a stabiliz aqueous suspension with sodium citrate buffer and approximat 7 mg. lecithin, 2 mg. carboxymethylcellulose, 3 mg. povid 0.5 mg. sorbitan monopalmitate, 0.5 mg. polyoxyethylene sorb monopalmitate, 1.2 mg. methylparaben, and 0.14 mg. pro paraben.

Five are graduating with honors. How many with VD?

On the average, you can figure the incidence of VD among teenagers at about 900 per 100,000 population.* And growing.

Among those in the 20-24 age-group, the incidence is even higher. And it, too, is growing.

In the long run, a populace educated to the risks and prevention of VD is probably the best answer to the problem. Meanwhile, though, adequate doses of the recommended types of penicillin remain a formidable weapon.

IN SYPHILIS

INJECTION

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STERILE BENZATHINE PENICILLIN G SUSPENSION) WYETH

Syphilis is preferably treated with benzathine penicillin G, which is also the drug of choice for prophylaxis after exposure. Administration of 2.4 million units (1.2 million in each buttock) usually cures most cases of primary, secondary and latent syphilis with negative spinal fluid.

Indications: In treatment of infections due to penicillin G-sensitive microorganisms that are susceptible to the low and very prolonged serum levels common to this particular dosage form. Therapy should be guided by bacteriological studies (including sensitivity tests) and by clinical response.

The following infections will usually respond to adequate dosage of intramuscular benzathine penicillin G.—Venereal infections: Syphilis, yaws, bejel and pinta.

For deep intramuscular injection only.

Contraindications: Previous hypersensitivity reaction to any penicillin.

Warnings: Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported. Anaphylaxis is more frequent following parenteral therapy but has occurred with oral penicillins. These reactions are more apt to occur in individuals with history of sensitivity to multiple allergens.

Severe hypersensitivity reactions with cephalosporins have been well documented in patients with history of penicillin hypersensitivity. Before penicillin therapy, carefully inquire into previous hypersensitivity to penicillins, cephalosporins and other allergens. If allergic reaction occurs, discontinue drug and treat with usual agents, e.g., pressor amines, antihistamines and corticosteroids.

Precautions: Use cautiously in individuals with histories of significant allergies and/or asthma.

Carefully avoid intravenous or intraarterial use, or injection into or near major peripheral nerves or blood vessels, since such injection may produce neurovascular damage.

In streptococcal infections, therapy must be sufficient to eliminate the organism; otherwise the sequelae of streptococcal disease may occur. Take cultures following completion of treatment to determine whether streptococci have been eradicated.

Prolonged use of antibiotics may promote overgrowth of nonsusceptible organisms including fungi. Take appropriate measures should superinfection occur.

Adverse Reactions: Hypersensitivity reactions reported are skin eruptions (maculopapular to exfoliative dermatitis), urticaria and other serum sickness reactions, laryngeal edema and anaphylaxis. Fever and eosinophilia may frequently be only reaction observed. Hemolytic anemia, leucopenia, thrombocytopenia, neuropathy and nephropathy are infrequent and usually associated with high doses of parenteral penicillin.

As with other antisyphilitics, Jarisch-Herxheimer reaction has been reported.

Administration and Dosage: Venereal infections—

Syphilis—Primary, secondary and latent—2.4 million units (1 dose).

Late (tertiary and neurosyphilis)—2.4 million units at 7 day intervals for three doses.

Congenital—under 2 years of age, 50,000 units/Kg. body weight; ages 2-12 years, adjust dosage based on adult dosage schedule.

(Shake multiple-dose vial vigorously before withdrawing the desired dose.) Administer by **deep intramuscular injection** in the upper outer quadrant of the buttock. In infants and small children, the midlateral aspect of the thigh may be preferable. When doses are repeated, vary the injection site. Before injecting the dose, aspirate to be sure needle bevel is not in a blood vessel. If blood appears, remove the needle and inject in another site.

Composition: Units benzathine penicillin G (as active ingredient): 2,400,000 units in 4-cc. single dose disposable syringe. Each disposable syringe also contains in aqueous suspension with sodium citrate buffer, as w/v approximately 0.5% lecithin, 0.6% carboxymethylcellulose, 0.6% povidone, 0.1% methylparaben, and 0.01% propylparaben. 300,000 units per cc.—10-cc. multi-dose vial. Each cc. also contains sodium citrate buffer, approximately 6 mg. lecithin, 3 mg. povidone, 1 mg. carboxymethylcellulose, 0.5 mg. sorbitan monopalmitate, 0.5 mg. polyoxyethylene sorbitan monopalmitate, 1.2 mg. methylparaben, and 0.14 mg. propylparaben.

Wyeth Laboratories
Philadelphia, Pa. 19101

U.S. Dept. of Health, Education, and Welfare: VD Fact Sheet 1972. Publication No. (HSM) 73-8195.

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May 9-10, 1975

- Venereal Disease
- Hepatitis
- Arthritis
- Pulmonary Disease
- Vasectomy
- Neonatal and Pediatric Infection
- Infectious Diarrheas
- Intestinal Parasites

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CMA Member fee: $30 for each. Please make check payable to California Medical Association.

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A complete program and hotel reservation information will be sent to you upon receipt of your registration fee. Registration fee is 100 percent refundable provided notice of cancellation is submitted to CMA in writing five days prior to the program.

Putting out the fires of arthritic pain
Rheumatoid arthritis can sometimes spread like wildfire, with joint after joint going up inflamed: "The usual onset is manifested by spotty joint involvement but an acute onset of symmetrical polyarthritis may be noted."*
If aspirin fails, consider Butazolidin alka. Giving one capsule four times a day often provides prompt, pain-relieving, anti-inflammatory action to help restore joint mobility. The results you can get within a week can be maintained on as little as one or two capsules daily.
Serious side effects can occur. Select patients carefully (particularly the elderly) and follow them closely in line with the drug's precautions, warnings, contraindications and adverse reactions. For full details, please read the prescribing information. It's summarized on the back of this page.
Butazolidin® alka
Each capsule contains:
100 mg. phenylbutazone USP
100 mg. dried aluminum hydroxide gel USP
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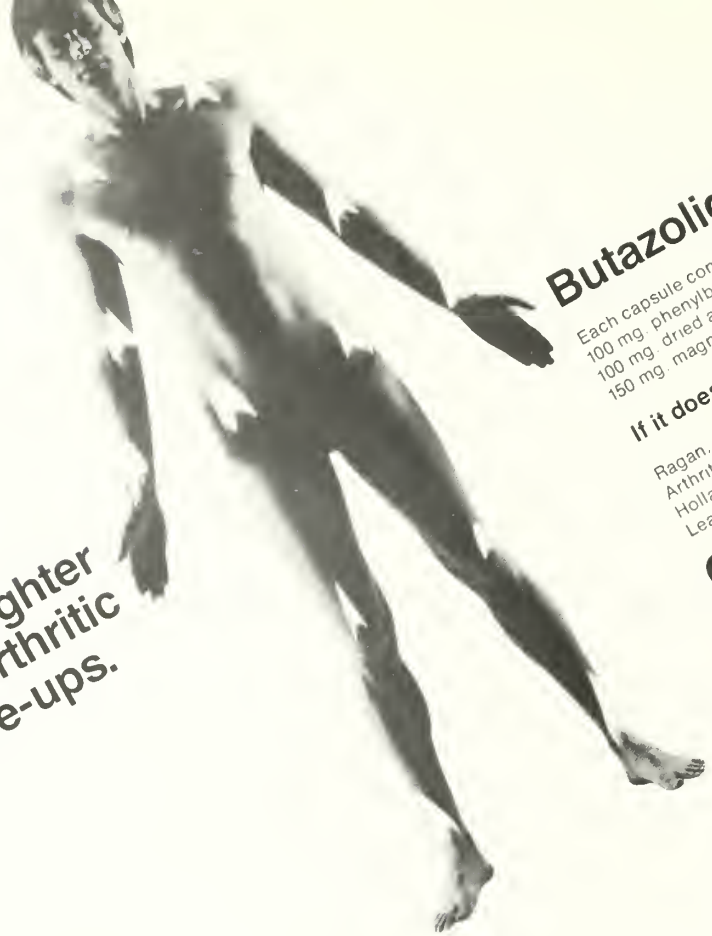
If it doesn't work in a week, forget it.



Butazolidin® alka

Each capsule contains:
100 mg. phenylbutazone USP
100 mg. dried aluminum hydroxide gel USP
150 mg. magnesium trisilicate USP

If it doesn't work in a week, forget it.

Ragan, C.: The Clinical Picture of Rheumatoid Arthritis, in Arthritis, ed. 8, edited by J. L. Hollander and D. J. McCarty, Jr., Philadelphia, Lea & Febiger, 1972, chap. 21, p. 335.

Geigy

Fire fighter for arthritic flare-ups.

Important Note This drug is not a simple analgesic. Do not administer casually. Carefully evaluate patients before starting treatment and keep them under close supervision. Obtain a detailed history, and complete physical and laboratory examination (complete hemogram, urinalysis, etc.) before prescribing and at frequent intervals thereafter. Carefully select patients, avoiding those responsive to routine measures, contraindicated patients or those who cannot be observed frequently. Warn patients not to exceed recommended dosage. Short-term relief of severe symptoms with the smallest possible dosage is the goal of therapy. Dosage should be taken with meals or a full glass of milk. Substitute alka capsules for tablets if dyspeptic symptoms occur. Patients should discontinue the drug and report immediately any sign of: fever, sore throat, oral lesions (symptoms of blood dyscrasia), dyspepsia, epigastric pain, symptoms of anemia, black or tarry stools or other evidence of intestinal ulceration or hemorrhage, skin reactions, significant weight gain or edema. A one-week trial period is adequate. Discontinue in the absence of a favorable response. Restrict treatment periods to one week in patients over sixty.

Indications Rheumatoid arthritis, osteoarthritis, bursitis, acute gouty arthritis and rheumatoid spondylitis.

Contraindications Children 14 years or less, senile patients, history or symptoms of G.I. inflammation or ulceration including severe, recurrent or persistent dyspepsia, history or presence of drug allergy, blood dyscrasias, renal, hepatic or cardiac dysfunction, hypertension, thyroid disease, systemic edema, stomatitis and salivary gland enlargement due to the drug, polymyalgia rheumatica and temporal arteritis, patients receiving other potent chemotherapeutic agents, or long-term anticoagulant therapy.

Warnings Age, weight, dosage, duration of therapy, existance of concomitant diseases and concurrent potent chemotherapy affect incidence of toxic reactions. Carefully instruct and observe the individual patient, especially the aging (forty years and over) who have increased susceptibility to the toxicity of the drug. Use lowest effective dosage. Weigh initially unpredictable benefits against potential risk of severe, even fatal, reactions. The disease condition itself is unaltered by the drug. Use with caution in first trimester of pregnancy and in nursing mothers. Drug may appear in cord blood and breast milk. Serious, even fatal, blood dyscrasias, including aplastic anemia, may occur suddenly despite regular hemograms, and may become manifest days or weeks after cessation of drug. Any significant change in total white count, relative decrease in granulocytes, appearance of immature forms, or fall in hematocrit should signal immediate cessation of therapy and complete hematologic investigation. Unexplained bleeding involving CNS, adrenals, and G.I. tract has occurred. The drug may potentiate action of insulin, sulfonylurea, and sulfonamide-type agents. Carefully observe patients taking these agents. Nontoxic and toxic goiters and myxedema have been reported (the drug reduces iodine uptake by the thyroid). Blurred vision can be a significant toxic symptom worthy of a complete ophthalmological examination. Swelling of ankles or face in patients under sixty may be prevented by reducing dosage. If edema occurs in patients over sixty, discontinue drug.

Precautions The following should be accomplished at regular intervals: Careful detailed history for disease being treated and detection of earliest signs of adverse reactions, complete physical examination including check of patient's weight, complete weekly (especially for the aging) or an every two week blood check, pertinent laboratory studies. Caution patients about participating in activity requiring alertness and coordination, as driving a car, etc. Cases of leukemia have been reported in patients with a history of short- and long-term therapy. The majority of these patients were over forty. Remember that arthritic-type pains can be the presenting symptom of leukemia.

Adverse Reactions This is a potent drug, its misuse can lead to serious results. Review detailed information before beginning therapy. Ulcerative esophagitis, acute and reactivated gastric and duodenal ulcer with perforation and hemorrhage, ulceration and perforation of large bowel, occult G.I. bleeding with anemia, gastritis, epigastric pain, hematemesis, dyspepsia, nausea, vomiting and diarrhea, abdominal distention, agranulocytosis, aplastic anemia, hemolytic anemia, anemia due to blood loss including occult G.I. bleeding, thrombocytopenia, pancytopenia, leukemia, leukopenia, bone marrow depression, sodium and chloride retention, water retention and edema, plasma dilution, respiratory alkalosis, metabolic acidosis, fatal and nonfatal hepatitis (cholestasis may or may not be prominent), petechiae, purpura without thrombocytopenia, toxic pruritus, erythema nodosum, erythema multiforme, Stevens-Johnson syndrome, Lyell's syndrome (toxic necrotizing epidermolysis), exfoliative dermatitis, serum sickness, hypersensitivity angiitis (polyarteritis), anaphylactic shock, urticaria, arthralgia, fever, rashes (all allergic reactions require prompt and permanent withdrawal of the drug), proteinuria, hematuria, oliguria, anuria, renal failure with azotemia, glomerulonephritis, acute tubular necrosis, nephrotic syndrome, bilateral renal cortical necrosis, renal stones, ureteral obstruction with uric acid crystals due to uricosuric action of drug, impaired renal function, cardiac decompensation, hypertension, pericarditis, diffuse interstitial myocarditis with muscle necrosis, perivascular granulomata, aggravation of temporal arteritis in patients with polymyalgia rheumatica, optic neuritis, blurred vision, retinal hemorrhage, toxic amblyopia, retinal detachment, hearing loss, hyperglycemia, thyroid hyperplasia, toxic goiter, association of hyperthyroidism and hypothyroidism (causal relationship not established), agitation, confusional states, lethargy, CNS reactions associated with overdosage, including convulsions, euphoria, psychosis, depression, headaches, hallucinations, giddiness, vertigo, coma, hyperventilation, insomnia, ulcerative stomatitis, salivary gland enlargement.

(B)98-146-070-J (10/71)

For complete details, including dosage, please see full prescribing information.

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(Continued on Page 36)

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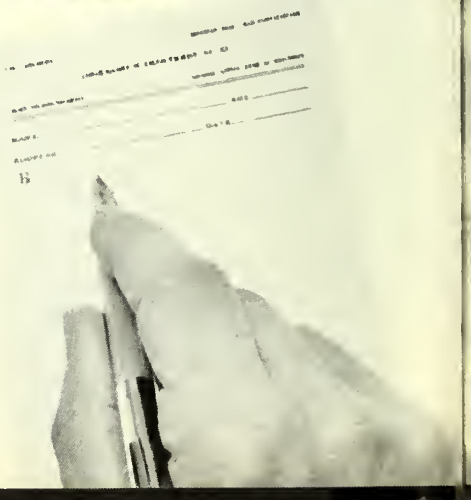
Bioequivalenc



he weight of scientific opinion:

If the pharmacist substituted a emically equivalent drug for the e you have specified for your tient—could you be certain of that oduct's safety and effectiveness nply because the chemical content as the same?

Definitely not, unless bio- uivalence tests and other quality surance checks had been conducted. he pharmaceutical industry and any scientists have maintained this sition for years, but others have estioned it. Now the Office of chnology Assessment of the ongress of the United States has ported on the issue in its Drug ioequivalence Study.*

Here are a few definitive state- ents in the O.T.A. report:

"...the problem of bioinequiva- ncy in chemically equivalent prod- cts is a real one. Since the studies in hich lack of bioequivalence was emonstrated involved marketed roducts that met current compen- ial standards, these documented in- ances constitute unequivocal vidence that neither the present andards for testing the finished roduct nor the specifications for aterials, manufacturing process, nd controls are adequate to ensure that ostensibly equivalent drug products are, in fact, equivalent in bioavailability.

"While these therapeutic failures resulting from problems of bioavailability were recognized and well documented, it is entirely possible that other therapeutic failures and/or instances of toxicity that had a similar basis have escaped attention."

The Pharmaceutical Manufacturers Association supports federal legislative amendments that would require manufacturers of duplicate prescription pharmaceutical products, subject to new drug procedures, to document:

(a) chemical equivalence; and (b) biological equivalence, where bioavailability test methods have been validated as a reliable means of assuring clinical equivalence; or (c) where such validation is not possible, therapeutic equivalence.

In addition, the PMA supports federal legislation that would require certification of all manufacturers of prescription products before they could start in business, annual inspections and certification thereafter, and strict adherence to FDA regulations on good manufacturing practices.

The overall quality of the United States drug supply is excellent. But only a total quality assurance program, envisaged in these and other policy positions adopted by the PMA Board of Directors in 1974, can bring about acceptable levels of performance by all prescription drug manufacturers and thereby assure the integrity of your prescription...

P·M·A

Pharmaceutical Manufacturers Association
1155 Fifteenth Street, N.W.
Washington, D.C. 20005

*Copies of the complete report on Drug Bioequivalence may be obtained from the Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402.

protecting the integrity of your prescription

(Continued from Page 32)

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Warnings: Do not use dietary potassium supplements or potassium salts unless hypokalemia develops or dietary potassium intake is markedly impaired. Enteric-coated potassium salts may cause small bowel stenosis with or without ulceration. Hyperkalemia (>5.4 mEq/L) has been reported in 4% of patients under 60 years, in 12% of patients over 60 years, and in less than 8% of patients overall. Rarely, cases have been associated with cardiac irregularities. Accordingly, **check serum potassium during therapy, particularly in patients with suspected or confirmed renal insufficiency (e.g., elderly or diabetics). If hyperkalemia develops, substitute a thiazide alone. If spironolactone is used concomitantly with 'Dyazide', check serum potassium frequently**—both can cause potassium retention and sometimes hyperkalemia. Two deaths have been reported in patients on such combined therapy (in one, recommended dosage was exceeded; in the other, serum electrolytes were not properly monitored). Observe patients on 'Dyazide' regularly for possible blood dyscrasias, liver damage or other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving Dyrenium (triamterene, SK&F). Rarely, leukopenia, thrombocytopenia, agranulocytosis, and aplastic anemia have been reported with the thiazides. Watch for signs of impending coma in acutely ill cirrhotics. Thiazides are reported to cross the placental barrier and appear in breast milk. This may result in fetal or neonatal hyperbilirubinemia, thrombocytopenia, altered carbohydrate metabolism and possibly other adverse reactions that have occurred in the adult. When used during pregnancy or in women who might bear children, weigh potential benefits against possible hazards to fetus.

Precautions: Do periodic serum electrolyte and BUN determinations. Do periodic hematologic studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in post-sympathectomy patients. The following may occur: hyperuricemia and gout, reversible nitrogen retention, decreasing alkali reserve with possible metabolic acidosis, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), digitalis intoxication (in hypokalemia). Use cautiously in surgical patients. Concomitant use with antihypertensive agents may result in an additive hypotensive effect.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis; rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting (may indicate electrolyte imbalance), diarrhea, constipation, other gastrointestinal disturbances. Rarely, necrotizing vasculitis, paresthesias, icterus, pancreatitis, and xanthopsia have occurred with thiazides alone.

Supplied: Bottles of 100 capsules; in Single Unit Packages of 100 (intended for institutional use only).

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CONTINUING MEDICAL EDUCATION

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COMMITTEE ON CONTINUING MEDICAL EDUCATION

THIS BULLETIN of information regarding continuing education programs and meetings of various medical organizations In **California and Hawaii** is supplied by the Committee on Continuing Medical Education of the California Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Committee on Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103; or phone (415) 777-2000. Note: Please see **California Medicine,** Vol. 117, No. 4, October, 1972 issue for a list of organizations approved for Category 1 Credit toward the CMA Certificate in Continuing Medical Education.

CANCER

March 19—**Clinical Aspects of Malignant Neoplasms.** Eden Hospital of Castro Valley at Oakland Airport Hilton Hotel. Wednesday. $35. Contact: Manard Pont, MD, Eden Hospital, 20103 Lake Chabot Rd., Castro Valley 94546. (415) 537-1234.

March 20-21—**Clinical Cancer Conference—10th Annual.** UCSF at St. Francis Hotel, San Francisco. Thursday-Friday.

May 7—**American Society of Clinical Oncology.** Town and Country Hotel, San Diego. Wednesday. Contact: Audrey E. Evans, MD, Children's Hospital of Philadelphia, 3400 Civic Ctr. Blvd., Philadelphia, Pa. 19104. (215) 387-6000.

May 8-10—**American Association for Cancer Research, Inc.—66th Annual Meeting.** Town and Country Hotel, San Diego. Thursday-Saturday. Contact: Hugh J. Creech, MD, AACR, 7701 Burholme Ave., Fox Chase, Philadelphia, Pa. 19111. (215) 342-1000, ext. 420.

May 28-30—**Cancer. USC.** Wednesday-Friday.

MEDICINE

March 15-16—**Echocardiography.** UCLA. Saturday-Sunday.

March 20-21—**Arthritis and Clinical Immunology.** USC. Thursday-Friday.

March 21—**Cerebrovascular Disease: Prevention and Diagnosis.** PMC. $60.

March 21-22—**Infectious Disease.** UCLA. Friday-Saturday.

March 27-29—**Recent Advances in Coronary Heart Disease.** UCI and Pasadena Cardiovascular Research Foundation at Balboa Bay Club, Newport Beach. Thursday-Saturday.

March 31-April 11—**Intensive Review of Internal Medicine.** USC. Two weeks.

April 2—**Sudden Death and Coronary Disease: Diagnostic and Therapeutic Interventions—12th Annual Spring Symposium.** American Heart Association-Greater Los Angeles Affiliate at Beverly Hilton Hotel, Beverly Hills. Wednesday. Contact: LaVerna Titus, AHA-Greater L.A. Affiliate, 2405 W. 8th St., Los Angeles 90057. (213) 385-4231.

April 3-4—**California Thoracic Society.** Sheraton Inn-Harbor Island Hotel, San Diego. Thursday-Friday. Contact: Laurie Harkness, CTS, 224 Pendleton Way, Oakland 94621. (415) 636-1756.

April 6-9—**What's New in Gastroenterology.** UCLA at Canyon Hotel, Palm Springs. Sunday-Wednesday.

April 7-10—**American College of Physicians—56th Annual Session.** Fairmont Hotel, San Francisco. Monday-Thursday. Contact: Edward C. Rosenow, Jr., MD, Exec. VP, ACP, 4200 Pine St., Philadelphia, Pa. 19104. (215) 222-8120.

April 7-16—**Cardiology for the Consultant: A Clinician's Retreat.** American College of Cardiology at Rancho Santa Fe Inn, Rancho Santa Fe. 10 days. Contact: Mary Anne McInerny, Dir., Dept. of Cont. Ed. Programs, 9650 Rockville Pike, Bethesda, Md. 20014. (301) 530-1600.

April 13-14—**American College of Physicians, Hawaii Regional Meeting.** Honolulu. Sunday-Monday. Contact: Bernard W. D. Fong, MD, 97 Dowsett Ave., Honolulu 96817.

April 15-18—**Consultants' Course in Dermatology.** UCSF. Tuesday-Friday.

April 21-25—**Diagnostic and Therapeutic Skills in Internal Medicine.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. Monday-Friday.

April 23—**Symposium on Cardiovascular Disease—15th Annual.** Calif. Heart Association and N. T. Enloe Memorial

(Continued on Page 41)

KEY TO ABBREVIATIONS AND SYMBOLS

Medical Centers and CMA Contacts for Information

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103. (415) 777-2000.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Duane Dillman, PhD, Director, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 564-5911, ext. 391.

LLU: Loma Linda University
Contact: John E. Peterson, MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311.

PMC: Pacific Medical Center
Contact: Allen J. Enelow, MD, Chairman, Education Committee, Pacific Medical Center, P.O. Box 7999, San Francisco 94120. (415) 563-4321.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Neil C. Andrews, MD, Chairman, Department of Postgraduate Medicine, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, California College of Medicine, Irvine
Contact: Robert Combs, MD, Associate Dean, Continuing Medical Education, University of California, Irvine—California College of Medicine, Irvine 92664. (714) 833-5991.

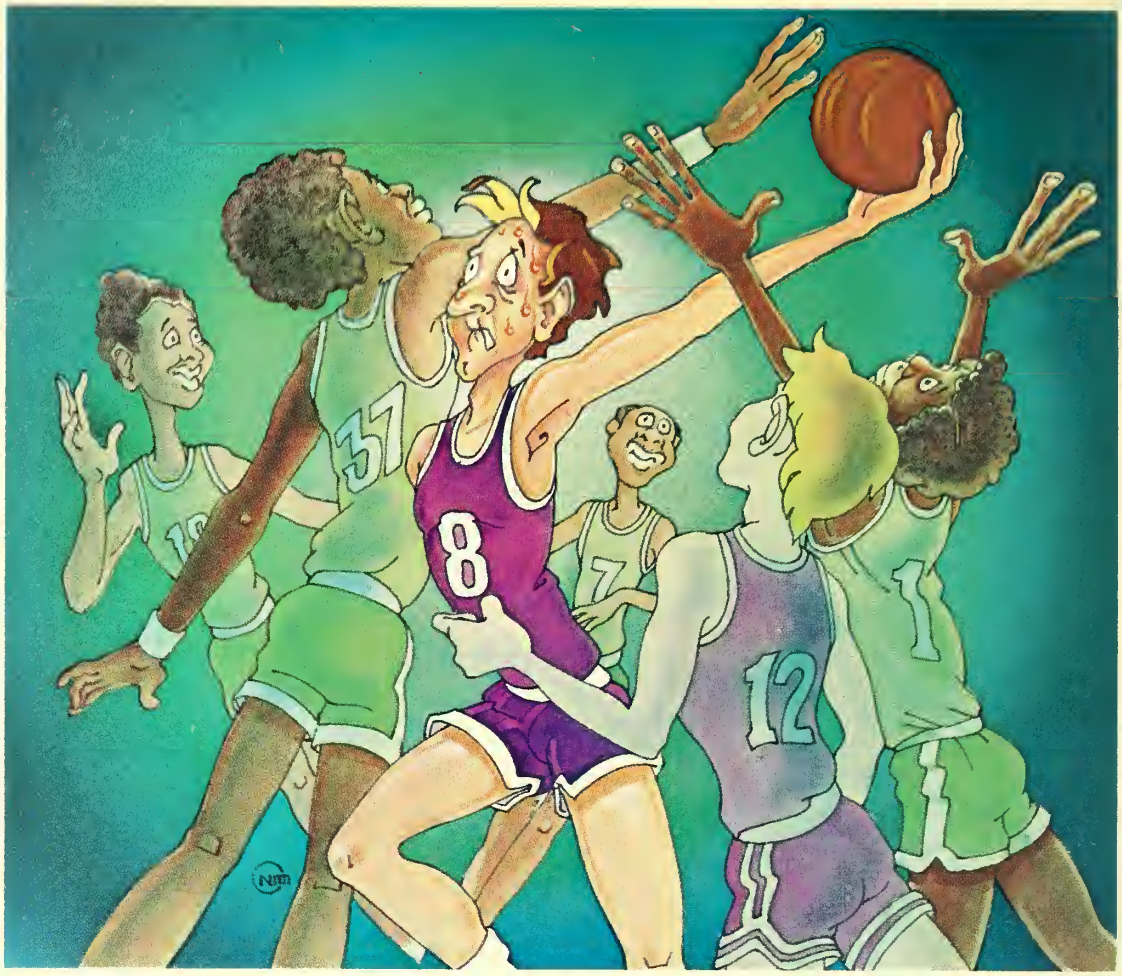
UCLA: University of California, Los Angeles
Contact: Donald Brayton, MD, Director Continuing Education in Medicine and the Health Sciences. P.O. Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: Richard A. Lockwood, MD, Associate Dean for Health Manpower, 1310 Basic Sciences Building, University of California, San Diego, School of Medicine, La Jolla 92037. (714) 453-2000, ext. 1251.

UCSF: University of California, San Francisco
Contact: Malcolm S. M. Watts, MD, Associate Dean and Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-2342.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 226-2047.

When diarrhea has his number...



Lomotil puts him back in the game.

Physicians and patients both want prompt control of the symptoms of diarrhea. A rapid, uncontrolled loss of fluids and electrolytes can cause a medical crisis, particularly in children, and in patients who are seriously ill, or in people who are badly undernourished.

Lomotil usually stops diarrhea promptly. This rapid action halts the emergency aspect of diarrhea and is comforting and reassuring to the patient. Electrolyte and fluid losses can be corrected while the specific cause of the diarrhea is being determined. If an infective agent is the cause, appropriate antibiotic therapy should be given along with Lomotil.

Lomotil has few side effects, and those that do occur are generally mild.

Lomotil®
TABLETS/LIQUID

Each tablet and each 5 ml. of liquid contain:
diphenoxylate hydrochloride ..... 2.5 mg.
(Warning: May be habit forming)
atropine sulfate ..... 0.025 mg.

Usually stops diarrhea promptly.

IMPORTANT INFORMATION: This is a Schedule V substance by Federal law; diphenoxylate HCl is chemically related to meperidine. In case of overdosage or individual hypersensitivity, reactions similar to those after meperidine or morphine overdosage may occur; treatment is similar to that for meperidine or morphine intoxication (prolonged and careful monitoring). Respiratory depression may recur in spite of an initial response to Nalline® (nalorphine HCl) or may be evidenced as late as 30 hours after ingestion. LOMOTIL IS NOT AN INNOCUOUS DRUG AND DOSAGE RECOMMENDATIONS SHOULD BE STRICTLY ADHERED TO, ESPECIALLY IN CHILDREN. THIS MEDICATION SHOULD BE KEPT OUT OF REACH OF CHILDREN.

Indications: Lomotil is effective as adjunctive therapy in the management of diarrhea.

Contraindications: In children less than 2 years, due to the decreased safety margin in younger age groups, and in patients who are jaundiced or hypersensitive to diphenoxylate HCl or atropine.

Warnings: Use with caution in young children, because of variable response, and with extreme caution in patients with cirrhosis and other advanced hepatic disease or abnormal liver function tests, because of possible hepatic coma. Diphenoxylate HCl may potentiate the action of barbiturates, tranquilizers and alcohol. In theory, the concurrent use with monoamine oxidase inhibitors could precipitate hypertensive crisis.

Usage in pregnancy: Weigh the potential benefits against possible risks before using during pregnancy, lactation or in women of childbearing age. Diphenoxylate HCl and atropine are secreted in the breast milk of nursing mothers.

Precautions: Addiction (dependency) to diphenoxylate HCl is theoretically possible at high dosage. Do not exceed recommended dosages. Administer with caution to patients receiving addicting drugs or known to be addiction prone or having a history of drug abuse. The subtherapeutic amount of atropine is added to discourage deliberate overdosage; strictly observe contraindications, warnings and precautions for atropine; use with caution in children since signs of atropinism may occur even with the recommended dosage.

Adverse reactions: Atropine effects include dryness of skin and mucous membranes, flushing and urinary retention. Other side effects with Lomotil include nausea, sedation, vomiting, swelling of the gums, abdominal discomfort, respiratory depression, numbness of the extremities, headache, dizziness, depression, malaise, drowsiness, coma, lethargy, anorexia, restlessness, euphoria, pruritus, angioneurotic edema, giant urticaria and paralytic ileus.

Dosage and administration: ***Lomotil is contraindicated in children less than 2 years old.*** Use only Lomotil liquid for children 2 to 12 years old. For ages 2 to 5 years, 4 ml. (2 mg.) t.i.d.; 5 to 8 years, 4 ml. (2 mg.) q.i.d.; 8 to 12 years, 4 ml. (2 mg.) 5 times daily; adults, two tablets (5 mg.) t.i.d. to two tablets (5 mg.) q.i.d. or two regular teaspoonfuls (10 ml., 5 mg.) q.i.d. Maintenance dosage may be as low as one fourth of the initial dosage. Make downward dosage adjustment as soon as initial symptoms are controlled.

Overdosage: Keep the medication out of the reach of children since accidental overdosage may cause severe, even fatal, respiratory depression. Signs of overdosage include flushing, lethargy or coma, hypotonic reflexes, nystagmus, pinpoint pupils, tachycardia and respiratory depression which may occur 12 to 30 hours after overdose. Evacuate stomach by lavage, establish a patent airway and, when necessary, assist respiration mechanically. Use a narcotic antagonist in severe respiratory depression. Observation should extend over at least 48 hours.

Dosage forms: *Tablets*, 2.5 mg. of diphenoxylate HCl with 0.025 mg. of atropine sulfate. *Liquid*, 2.5 mg. of diphenoxylate HCl and 0.025 mg. of atropine sulfate per 5 ml. A plastic dropper calibrated in increments of ½ ml. (total capacity, 2 ml.) accompanies each 2-oz. bottle of Lomotil liquid.

SEARLE **Searle & Co.**
San Juan, Puerto Rico 00936

Address medical inquiries to:
G. D. Searle & Co.
Medical Department, Box 5110,
Chicago, Illinois 60680

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(Continued from Page 39)

Hospital at Elks Lodge Hall, Chico. Wednesday. 6 hrs. $25. Contact: Marge Herman, CHA, 1372 Longfellow Ave., Chico 95926. (916) 342-4247.

April 23-25—**Diabetes and Related Endocrine Diseases.** UCSF. Wednesday-Friday.

May 2—**The Thyroid.** PMC at Miyako Hotel, San Francisco. Friday. $80.

May 8—**Asthma.** USC. Thursday.

May 9-10—**Blood Transfusion—1975.** UCSF. Friday-Saturday.

May 19-23.—**Advances in Internal Medicine.** UCSF. Monday-Friday.

May 22-24—**Ischemic Heart Disease: A Critical Overview.** PMC and American College of Cardiology at St. Francis Hotel, San Francisco. Thursday-Saturday.

MENTAL RETARDATION

April 29-30—**Mental Retardation.** USC. Tuesday-Wednesday.

OBSTETRICS AND GYNECOLOGY

March 15-16—**Gynecologic Endoscopy: Diagnostic and Operative.** UCI and American Association of Gynecological Laparoscopists. Saturday-Sunday. $150.

March 25-28—**High Risk Pregnancy.** USC at Canyon Hotel, Palm Springs. Tuesday-Friday.

March 28-29—**Review of Gynecological Surgery.** PMC at Miyako Hotel, San Francisco. Friday-Saturday.

April 1—**Oral Contraceptives Symposium.** World Health Information Services, Inc, and USC at Century Plaza Hotel, Los Angeles. Tuesday. Contact: Yvonne Maddox, President, WHIS, 145 E. 49th St., New York 10017. (212) 751-5737.

April 2-5—**American Fertility Society.** Century Plaza Hotel, Los Angeles. Wednesday-Saturday. Contact: Robert B. Wilson, MD, Med. Dir., AFS, 1608 13th Ave. S., Suite 101, Birmingham, Ala. 35205. (205) 933-7222.

April 16-18—**Association of Planned Parenthood Physicians.** See Of Interest to All, April 16-18.

April 21-25—**Family Planning.** UCLA. Monday-Friday. Contact: Irvin M. Cushner, MD, Ob-Gyn Dept., UCLA Center for Health Sciences, Los Angeles 90024. (213) 825-1046.

May 16-17—**Obstetrics and Gynecology Symposium.** Southern Calif. Permanente Medical Group at Sheraton Hotel, Anaheim. Friday-Saturday. Contact: Shirley Gach, So. Calif. Permanente Medical Group, 4900 Sunset Blvd., Los Angeles 90027. (213) 667-4242.

May 19-22—**Ob/Endocrinology and Infertility.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. Monday-Thursday.

PEDIATRICS

April 4-5—**Pediatric Conference: Infectious Diseases in Childhood and Adolescent Medicine.** UCD at Mansion Inn, Sacramento. Saturday-Sunday.

April 5-12—**Pediatrics.** USC at Kona Surf Hotel, Kona, Hawaii. One week.

April 6-7—**Parenting/Pediatrics.** DREW. Sunday-Monday.

April 21-25—**Review of Pediatrics.** USC. Monday-Friday.

April 26—**Growth to Maturity: The Adolescent and the Helping Professions.** UCSF. Saturday.

May 2-3—**Pediatric Symposium.** Southern Calif. Permanente Medical Group. Friday-Saturday. Contact: Shirley Gach, So. Calif. Permanente Medical Group, 4900 Sunset Blvd., Los Angeles 90027. (213) 667-4242.

May 8-10—**Annual Pediatric Course.** UCSF. Thursday-Saturday.

May 16-18—**American Academy of Pediatrics, Northern California Chapter.** Ahwahnee Hotel, Yosemite. Friday-Sunday.

Contact: Melvin Schwartz, MD, 2219 Santa Clara Ave., Alameda 94501. (415) 523-3417.

May 17-18—**Hypertension in Children and Adolescents: Facts, Fictions and Controversies.** Memorial Hosp. Med. Ctr. of Long Beach, Children's Hosp. of Long Beach, Children's Hosp. of Los Angeles at Center for Health Education, Long Beach. Saturday-Sunday. Contact: Executive Secretary, Center for Health Education, 2801 Atlantic Ave., Long Beach 90801.

May 18-21—**Heart and Lung Disease in Neonates and Infants.** UCLA at Ahwahnee Hotel, Yosemite. Sunday-Wednesday.

May 31-June 1—**Attentional Disorders in Children.** UCLA at Asilomar Conference Grounds, Monterey. Saturday-Sunday.

PSYCHIATRY

April 9-June 25—**Advanced Psychotherapeutic Techniques—A Practical Approach to Therapy—Part II.** UCLA. Wednesdays, 7:30-10:00 p.m.

April 11-12—**AMA Department of Mental Health Conference.** St. Francis Hotel, San Francisco. Friday-Saturday. Contact: AMA Dept. of Mental Health, 535 N. Dearborn St., Chicago 60610. (312) 751-6000.

April 25—**Prevention and Indirect Services.** See Of Interest to All, April 25.

May 3-4—**American Society for Adolescent Psychiatry—Annual Meeting.** Century Plaza Hotel, Los Angeles. 9 hrs. $25 for members; $35, non-members. Contact: Mary D. Staples, ASAP, 24 Green Valley Rd., Wallingford, Pa. 19086. (215) 566-1054.

May 4—**American Academy of Psychiatry and the Law—Semi-Annual Meeting.** Anaheim. Sunday. Contact: Seymour Pollack, MD, USC Institute of Psychiatry and Law, 1237 N. Mission Rd., Los Angeles 90033.

May 5-9—**American Psychiatric Association.** Anaheim. Monday-Friday. Contact: Melvin Sabshin, MD, Med. Dir., APA, 1700 18th St., N.W., Washington, D.C. 20009.

May 17—**Suicide Prevention.** UCSF. Saturday.

May 21-26—**Psychiatric Update—2nd Annual.** UCLA at Ahwahnee Hotel, Yosemite. Wednesday-Monday.

RADIOLOGY AND PATHOLOGY

May 3—**Nuclear Medicine—5th Annual Spring Symposium.** Sierra Valley Nuclear Medicine Assn.; No. Calif. Chapter, Society of Nuclear Medicine, at El Rancho Hotel, West Sacramento. Saturday. Contact: Darleen Nelson, Nuclear Med. Dept., Mercy San Juan Hospital, 6501 Coyle Ave., Carmichael 95608.

SURGERY AND ANESTHESIOLOGY

March 15—**Surgical Anatomy and Surgery of the Abdomen.** International College of Surgeons, U.S. Section, at L.A. Orthopaedic Hospital, Los Angeles. Saturday. 8 hrs. $50. Contact: Irving Rehman, PhD, Chr., Postgraduate & Ongoing Education Committee, 5153 Tampa Ave., Tarzana 91356. (213) 344-3305.

March 15-16—**Los Angeles County Society of Anesthesiologists—20th Annual Postgraduate Assembly.** Hilton Hotel, Los Angeles. Saturday-Sunday. Contact: L.A. County Soc. of Anesthesiologists, 184 N. Canon Dr., Beverly Hills 90210.

March 15-19—**Controversial Areas in Surgery—12th Annual.** UCLA at Canyon Hotel, Palm Springs. Saturday-Wednesday.

March 16-28—**Temporal Bone Surgical Dissection Course.** Ear Research Institute, Los Angeles. Two weeks. $1,200; $900, residents. Contact: Jack L. Pulec, MD, 2130 W. 3rd St., L.A. 90057.

March 19-23—**Management of Trauma.** UCLA at Canyon Hotel, Palm Springs. Wednesday-Sunday.

March 20-21—**Diseases of the Urinary Tract: Techniques and Principles of Urologic Surgery—3rd Annual Symposium.** STAN. Thursday-Friday.

April 3-4—**Ophthalmology Symposium—Posterior Segment Complications of Anterior Segment Surgery.** Mt. Zion Hospital and Medical Center at St. Francis Hotel, San Francisco. Thursday-Friday. 16 hrs. $200. Contact: Linda Cross, Dept. of Cont. Ed., Mt. Zion Hospital, 1600 Divisadero, San Francisco 94115. (415) 567-6600, ext. 108.

April 3-4—**Phaco-Fragmentation.** UCSF. Thursday-Friday.

April 3-4—**California Thoracic Society.** See Medicine, April 3-4.

April 5-12—**Orthopedics.** USC at Mauna Kea Hotel, Kamuela, Hawaii. One week.

April 6-18—**Temporal Bone Surgical Dissection Course.** Ear Research Institute, Los Angeles. Two weeks. $1,200; $900 for residents. Contact: Jack L. Pulec, MD, Ear Research Institute, 2130 W. 3rd St., Los Angeles 90057.

April 7-10—**Care of Spinal Cord Injury Patients.** Rickey's Hyatt House, Palo Alto. Monday-Thursday. Contact: Inder Perkash, MD, Chief, Spinal Cord Injury Service, VA Hospital, 3801 Miranda Ave., Palo Alto 94304.

April 10-12—**General Surgery—Annual Conference.** UCSF at Hilton Hotel, San Francisco. Thursday-Saturday.

April 19—**Surgical and Clinical Anatomy of the Vascular System.** International College of Surgeons, U.S. Section, at L.A. Orthopaedic Hospital, Los Angeles. Saturday. 8 hrs. $50. Contact: Irving Rehman, PhD, Chr., Postgraduate and Ongoing Education Committee, International College of Surgeons, U.S. Section, 5153 Tampa Ave., Tarzana 91356. (213) 344-3305.

April 26-May 3—**Management of the Surgical Patient.** STAN at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week.

April 30-May 3—**Body Contouring and Reconstruction.** UCLA. Wednesday-Saturday.

May 2-3—**Microsurgery of the Anterior Segment of the Eye—6th Annual Jules Stein Lecture and Postgraduate Seminar.** UCLA. Friday-Saturday.

May 2-3—**Trauma.** UCSF at Mary's Help Hospital, San Francisco. Friday-Saturday.

May 4-8—**American Society of Colon and Rectal Surgeons.** Hilton Hotel, San Francisco. Sunday-Thursday. 20 hrs. Contact: Harriette Gibson, Admin. Sec., ASCRS, 320 W. Lafayette, Detroit, Mi. 48226. (313) 961-7880.

May 4-11—**14th Biennial Western Conference on Anesthesiology.** Princess Kaiulani Hotel, Honolulu. One week. Contact: Murray G. Atnikov, MD, Sec-Treas, BWCA Travel Headquarters, P.O. Box 32366, San Antonio, Tex. 78216.

May 8—**Industrial Back Injuries.** PMC. Thursday.

May 9—**Office Orthopedics.** USC. Friday.

May 15-17—**Neurosurgery.** UCSF and American College of Surgeons at Hilton Hotel, San Francisco. Thursday-Saturday.

May 17—**American College of Surgeons, Northern California Chapter.** Hilton Hotel, San Francisco. Saturday. Contact: Dorothy Archbold, Exec. Sec., 2249 Van Ness Ave., No. 2, San Francisco 94109. (415) 221-4810, ext. 251

May 17—**Surgical Anatomy and Surgery of the Chest.** International College of Surgeons, U.S. Section, at Los Angeles Orthopaedic Hospital. Saturday. 8 hrs. $50. Contact: Irving Rehman, PhD, Chr., Postgraduate and Ongoing Education Committee, 5153 Tampa Ave., Tarzana 91356. (213) 344-3305.

May 22-23—**Phaco-Fragmentation.** UCSF. Thursday-Friday.

May 22-23—**Sensory and Perceptual Dysfunction.** USC. Thursday-Friday.

OF INTEREST TO ALL PHYSICIANS

March 21-22—**West Coast Counties Postgraduate Institute.** CMA at Quail Lodge, Carmel. Friday-Saturday.

March 22-23—**Healing I.** UCSC; UCLA and Gladman Memorial Hospital, Oakland, at Univ. of Calif., Santa Cruz. Saturday-Sunday. Contact: UC Extension, Santa Cruz 95064.

March 23-27—**American Association of Anatomists.** Hilton Hotel, Los Angeles. Sunday-Thursday. Contact: Dr. Melvin Hess, Dept. of Anatomy, La. State Univ. Med. Center, 1542 Tulane Ave., New Orleans, La. 70112.

April 4-5—**Course in Diving Medicine for the Practicing Physician.** UCSF at Sheraton-Palace Hotel, San Francisco. Friday-Saturday. 16 hrs. $125.

April 6-10—**The Family in Family Practice.** UCLA at Riviera Hotel, Palm Springs. Sunday-Thursday.

April 7-10—**Care of Spinal Cord Injury Patients.** See Surgery, April 7-10.

April 12-13—**Healing II.** UCSC; UCLA and Gladman Memorial Hospital, Oakland, at Univ. of Calif., Santa Cruz. Saturday-Sunday. Contact: UC Extension, Santa Cruz 95064.

April 13-17—**American Industrial Health Conference.** American Occupational Medical Association at Hilton Hotel, San Francisco. Sunday-Thursday. 18 hrs. $30. Contact: Howard N. Schulz, Exec. Dir., AOMA, 150 N. Wacker Dr., Chicago, Ill. 60606. (312) 782-2166.

April 14-20—**Introduction to Diving Medicine.** UCSF at VA Hospital, Fresno. Monday-Sunday.

April 15—**Assault or Negligence: Doctor's Choice.** UCSF. Tuesday

April 16-18—**Association of Planned Parenthood Physicians—13th Annual Scientific Meeting and Postgraduate Program.** Century Plaza Hotel, Los Angeles. Wednesday-Friday. Contact: Joseph E. Davis, MD, 810 7th Ave., N.Y. 10019. (212) 541-7800.

April 17-18—**Obesity.** USC. Thursday-Friday.

April 19-20—**Ethical Issues in Modern Medical Practice.** UCLA. Saturday-Sunday.

April 21-25—**Emergency Medicine.** USC at Kona Surf Hotel, Kona, Hawaii. Monday-Friday.

April 21-25—**Family Planning.** See Ob-Gyn, April 21-25.

April 21-May 2—**Emergency Department Medicine in Practice.** UCLA and Harbor General Hospital at Harbor Gen. Hosp., Torrance. Two weeks.

April 25—**Prevention and Indirect Services.** Kings View Foundation at Sheraton Inn, Fresno. Friday. $20. Directed to physicians interested in various aspects of prevention in fields of mental health, developmental disabilities, substance abuse and gerontology. Contact: Kings View Foundation, Public Information Dept., P.O. Box 512, Reedley 93654. (209) 638-3655.

April 25-26—**Human Sexuality and Medicine.** CMA at Ahwahnee Hotel, Yosemite. Friday-Saturday.

April 25-26—**Medical Applications of Behavior Modification to Stroke, Heart Disease, Spinal Injury and Cancer.** PMC. Friday-Saturday. $125.

April 25-27—**Advances in the Control & Management of Chronic Pain.** UCLA. Friday-Sunday.

April 28-May 1—**Aerospace Medical Association—46th Annual Scientific Meeting.** Hilton Hotel, San Francisco. Monday-Thursday. 18 hrs. Contact: Merrill H. Goodwin, MD, Exec. VP, Aerospace Med. Assn., Washington National Airport, Washington, D.C. 20001. (202) 638-2190.

May 2—**The Thyroid.** See Medicine, May 2.

May 9-10—**San Joaquin Valley Counties Postgraduate Institute.** CMA at Ahwahnee Hotel, Yosemite. Friday-Saturday.

May 10—**Clinical Pharmacology Conference — 6th Annual.** STAN at Palo Alto Medical Research Foundation, Palo Alto. Saturday.

May 19-23—**Topics in Emergency Medicine.** UCSF. Monday-Friday.

PRECEPTORSHIPS AND TRAINEESHIPS

Training for Physicians in General Internal Medicine. LLU. Four weeks or more, by arrangement. Bedside and classroom training, practical aspects of clinical care and management. 160 hrs. Contact: John E. Peterson, MD, LLU.

Training of Physicians in Modern Concepts of Pulmonary Care. LLU. Four weeks or more, by arrangement. Diagnostic and therapeutic methods in medical chest disease, physiological methodology of modern pulmonary care programs, use of new instrumentation in the field. 160 hrs. Contact: John E. Hodgkin, MD, Chief, Section of Medical Chest Diseases, LLU.

Training for Physicians in Nephrology. LLU. Four weeks or more, by arrangement. Hemodialysis, peritoneal displays, renal biopsy, and kidney transplantation. 160 hrs. Contact: Robert E. Soderblom, MD, LLU.

Mini Residencies in Orthopaedics. STAN. Postgraduate traineeships of 4-14 days, as you wish. No tuition but donations accepted. Contact: Orthopaedic Division, Dept. of Surgery, Stanford.

Preceptorships in Cardiology. PMC. By arrangement. $200 per mo.; $500 for 3 mos. Contact: Arthur Selzer, MD, PMC.

Preceptorships in Practical Office Dermatology. PMC. Wednesdays or Fridays, 9:00 a.m.-12:00 noon, for 10 weeks. Periods begin Oct., Jan., or April. $100. Contact: Harold M. Schneidman, MD, Dept. of Dermatology, PMC.

Preceptorships in Infectious Disease. PMC. Full time for four weeks. To be arranged. $250. Contact: Rodney J. Valentine, MD, Chief, Div. of Infectious Diseases, PMC.

Preceptorships in Basic Sciences, Biochemistry and Biophysics, Dermatology, Echocardiography, International Health, Microbiology, Neurological Surgery, Obstetrics and Gynecology, Pediatrics, Pharmacology and Experimental Therapeutics, Physiology, Psychiatry, Urology. UCSF. By special arrangement.

Traineeships in Renal Dialysis. UCSF. By special arrangement.

AUDIO-DIGEST FOUNDATION

A non-profit subsidiary of CMA. Twice-a-month tape recorded summaries of leading national meetings and surveys of current literature. Services by subscription in: Family Practice, Surgery, Internal Medicine, Ob/Gyn, Pediatrics, Psychiatry, Anesthesiology, Ophthalmology, Otorhinolaryngology. Catalog of lectures and panel discussions in all areas of medical practice also available. $75 per year. Contact: Mr. Claron L. Oakley, Editor, Suite 700, 1930 Wilshire Blvd., Los Angeles 90057. (213) 483-3451.

OREGON

COUNCIL ON MEDICAL EDUCATION

THIS BULLETIN of information regarding continuing education programs and meetings of various medical organizations in Oregon is supplied by the Council on Medical Education of the Oregon Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Council on Medical Education, Oregon Medical Association, 2164 S.W. Park Place, Portland, Oregon 97205; or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

University of Oregon Medical School, Family Practice Center, 3181 S.W. Sam Jackson Park Road, Portland 97201:

Every Thursday, 8:00 a.m. to 9:00 a.m.—**Family Practice Grand Rounds.** Contact: David D. Smith, MD, Department of Family Practice, University of Oregon Medical School.

Providence Hospital, 700 N.E. 47th Ave., Portland 97213 (Contact: Marian Campbell, Department of Medical Education, 503-234-8211):

March 19, Wednesday, 8:00 a.m. (Auditorium, Providence Hall)—**Medical Morbidity and Mortality**—W. Miller, MD, Chief Medicine Resident, and W. Olsen, MD, Chairman, Medical Committee.

ANESTHESIOLOGY

May 17-19—**Oregon Society of Anesthesiologists, Inc. Annual Meeting.** Salishan, Gleneden Beach, Oregon 97388. Contact: Lynn Husband, MD, 2212 N.W. Pettygrove, Portland 97210.

CARDIOLOGY

June 5-7—**Progress in Coronary Artery Disease and Valvular Heart Disease.** Portland. Contact: S. H. Rahimtoola, University of Oregon Medical School, 3181 S.W. Sam Jackson Park Road, Portland 97201.

FAMILY PRACTICE

Every Thursday, 8:00 a.m. to 9:00 a.m.—**Family Practice Grand Rounds.** Family Practice Center, University of Oregon Medical School, Portland. Contact: David D. Smith, MD, Department of Family Practice, University of Oregon Medical School, 3181 S.W. Sam Jackson Park Road, Portland 97201.

May 1-4—**Oregon Academy of Family Practice 28th Annual Scientific Assembly.** Jantzen Beach Thunderbird, Portland. Contact: Ms. Skippie Patterson, Oregon Academy of Family Practice, 2153 S.W. Main, Portland 97205.

INTERNAL MEDICINE

May 15-17—**Oregon Society of Internal Medicine Annual Meeting.** Inn of the Sevnth Mountain, Bend. Contact: Ted Lawson, Oregon Society of Internal Medicine, 2164 S.W. Park Place, Portland 97205.

NEUROLOGY

June 7-8—**Oregon Neurosurgical Society Annual Meeting.** Jantzen Beach Thunderbird, Portland. Contact: Michael Mason, MD, 2525 N.W. Lovejoy, Portland 97210.

OPHTHALMOLOGY AND OTOLARYNGOLOGY

March 14-15—**Oregon Academy of Ophthalmology and Otolaryngology Annual Meeting.** Sheraton Motor Inn, Portland. Contact: Richard Panian, MD, 2222 N.W. Lovejoy, Suite 423, Portland 97210.

PEDIATRICS

March 12-15—**North Pacific Pediatric Society Annual Meeting.** Portland. Contact: B. C. DeLong, MD, 3195 Granville St., Suite 106, Vancouver, B.C., Canada.

PSYCHIATRY

April 6—**American Psychiatric Association, Oregon District Branch Annual Meeting.** Jantzen Beach Thunderbird, Portland. Contact: Clement C. Vickery, MD, 740 Winter Street, S.E., Salem 97301.

OF INTEREST TO ALL PHYSICIANS

May 30-31—**Hypertension: The Challenge to the Clinician.** Portland, Jantzen Beach Thunderbird. Sponsored by the University of Oregon Medical School. Contact: M. Roberts Grover, Jr., MD, Associate Dean, University of Oregon Medical School, 3181 SW Sam Jackson Park Road, Portland 97201, (503) 225-8228. Acceptable for 10 hours Category I credit.

(Continued on Page 46)

PROLOID® (thyroglobulin)
Caution: Federal law prohibits dispensing without prescription.
Description. Proloid (thyroglobulin) is obtained from a purified extract of frozen hog thyroid. It contains the known calorigenically active components, Sodium Levothyroxine (T_4) and Sodium Liothyronine (T_3). Proloid (thyroglobulin) conforms to the primary USP specifications for desiccated thyroid—for iodine based on chemical assay—and is also biologically assayed and standardized in animals.
Chromatographic analysis to standardize the Sodium Levothyroxine and Sodium Liothyronine content of Proloid (thyroglobulin) is routinely employed.
The ratio of T_4 and T_3 in Proloid (thyroglobulin) is approximately 2.5 to 1.
Proloid (thyroglobulin) is stable when stored at usual room temperature.
Indications. Proloid (thyroglobulin) Is thyroid replacement therapy for conditions of inadequate endogenous thyroid production: e.g., cretinism and myxedema. Replacement therapy will be effective only in manifestations of hypothyroidism.
In simple (nontoxic) goiter, Proloid (thyroglobulin) may be tried therapeutically, in nonemergency situations, in an attempt to reduce the size of such goiters.
Contraindication. Thyroid preparations are contraindicated in the presence of uncorrected adrenal insufficiency.
Warnings. Thyroglobulin should not be used in the presence of cardiovascular disease unless thyroid-replacement therapy is clearly indicated. If the latter exists, low doses should be instituted beginning at 0.5 to 1.0 grain (32 to 64 mg) and increased by the same amount in increments at two-week intervals. This demands careful clinical judgment.
Morphologic hypogonadism and nephroses should be ruled out before the drug is administered. If hypopituitarism is present, the adrenal deficiency must be corrected prior to starting the drug.
Myxedematous patients are very sensitive to thyroid and dosage should be started at a very low level and increased gradually.
Precaution. As with all thyroid preparations this drug will alter results of thyroid function tests.
Adverse Reactions. Overdosage or too rapid increase in dosage may result in signs and symptoms of hyperthyroidism, such as menstrual irregularities, nervousness, cardiac arrhythmias, and angina pectoris.
Dosage and Administration. Optimal dosage is usually determined by the patient's clinical response. Confirmatory tests include BMR, $T_3{}^{131}I$ resin sponge uptake, $T_3{}^{131}I$ red cell uptake, Thyro Binding Index (TBI), and Achilles Tendon Reflex Test. Clinical experience has shown that a normal PBI (3.5-8 mcg/100 ml) will be obtained in patients made clinically euthyroid when the content of T_4 and T_3 is adequate. Dosage should be started in small amounts and increased gradually with increments at intervals of one to two weeks. Usual maintenance dose is 0.5 to 3.0 grains (32 to 190 mg) daily.
Instructions for Use. The following conversion table lists the approximate equivalents of other thyroid preparations to Proloid (thyroglobulin) when changing medication from desiccated thyroid, T_4 (sodium levothyroxine), T_3 (sodium liothyronine), or T_4/T_3 (liotrix).

CONVERSION TABLE

Dose of Proloid (thyroglobulin)	Dose of Desiccated Thyroid	Dose of T_4 (sodium levothyroxine)	Dose of T_3 (sodium liothyronine)	Dose of liotrix (T_4/T_3)
1 grain	1 grain	0.1 mg	25 mcg	#1 (60 mcg/15 mcg)
2 grains	2 grains	0.2 mg	50 mcg	#2 (120 mcg/30 mcg)
3 grains	3 grains	0.3 mg	75 mcg	#3 (180 mcg/45 mcg)
4 grains	4 grains	0.4 mg	100 mcg	
5 grains	5 grains	0.5 mg	125 mcg	

In changing from Thyroid USP to Proloid (thyroglobulin), substitute the equivalent dose of Proloid (thyroglobulin). Each patient may still require fine adjustment of dosage because the equivalents are only estimates.
Overdosage Symptoms. Headache, instability, nervousness, sweating, tachycardia, with unusual bowel motility. Angina pectoris or congestive heart failure may be induced or aggravated. Shock may develop. Massive overdosage may result in symptoms resembling thyroid storm. Chronic excessive dosage will produce the signs and symptoms of hyperthyroidism.
(Treatment: In shock, supportive measures should be utilized. Treatment of unrecognized adrenal insufficiency should be considered.)
Supplied. ¼ grain tablets in bottles of 100 (N 0047-0250-51) and 1000 (N 0047-0250-60); ½ grain tablets in bottles of 100 (N 0047-0251-51) and 1000 (N 0047-0251-60); scored 1 grain tablets in bottles of 100 (N 0047-0252-51) and 1000 (N 0047-0252-60); 1½ grain tablets in bottles of 100 (N 0047-0253-51) and 1000 (N 0047-0253-60); scored 2 grain tablets in bottles of 100 (N 0047-0257-51); 3 grain tablets in bottles of 100 (N 0047-0254-51) and 1000 (N 0047-0254-60); scored 5 grain tablets in bottles of 100 (N 0047-0255-51) and 1000 (N 0047-0255-60). Full information is available on request. P-GP-51 4/c

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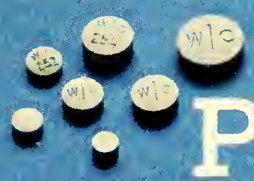

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all the qualities of the "natural" with the
added improvements of man...

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natural thyroid...but uniquely purified
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natural thyroid...but triply standardized
Standardized chemically, biologically, and (at intervals) clinically, for consistent metabolic activity from batch to batch.

natural thyroid...but consistently fresh
Potency undiminished for up to 4 years under proper storage conditions.

It all adds up to natural thyroid with the added improvements of man.

Please see adjoining column for brief summary of prescribing information.

(Continued from Page 44)

WASHINGTON, MONTANA, ALASKA and IDAHO

In order to have future activities listed here or to receive information on these and other activities, please write Ms. Joan M. Kelday, Information Specialist, Continuing Medical Education, WAMI Program, University of Washington School of Medicine, E-301, Health Sciences Building, SC-45, Seattle, Washington 98195. Phone: (206) 543-6995.

March 14-15—**Current Concepts in Cardiology.** Friday-Saturday. Virginia Mason Medical Center Auditorium, Seattle. 9 hrs. $50. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) MA 3-3700, Ext. 470.

March 17-21—**Emergency Medicine Institute.** Monday-Friday. Univ. of Wash. Health Sciences Center, Seattle. 40 hrs. $250. Contact: Richard L. Reimer, Asst. Dir. CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

March 20-21—**Basic Sciences for Clinicians.** Thursday-Friday. Univ. of Wash. Health Sciences Center, Seattle. 9 hrs. $55. Contact: Richard L. Reimer, Asst. Dir. CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

March 28-29—**Diabetic Patient Education: A Course for Physicians, Nurses and Allied Health Personnel.** Friday-Saturday. Virginia Mason Medical Center Auditorium, Seattle. 9 hrs. $50, physicians; $25, others. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) MA 3-3700, Ext. 470.

March 31-April 4—**Advances in Family Practice.** Monday-Friday. Univ. of Wash. Health Sciences Center, Seattle. 40 hrs. $100. Contact: Richard L. Reimer, Asst. Dir. CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

April 4-5—**Acid Base and Blood Gas Management in the Surgical Patient.** Friday-Saturday. Virginia Mason Medical Center Auditorium, Seattle. 9 hrs. $50. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) MA 3-3700, Ext. 470.

April 24-25—**Conference on Respiratory Care.** Thursday-Friday. Univ. of Wash. Health Sciences Center, Seattle. Hours not set. $75. Contact: Richard L. Reimer, Asst. Dir. CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

April 28-May 2—**Emergency Medicine Institute.** Monday-Friday. Univ. of Wash. Health Sciences Center, Seattle. 40 hrs. $250. Contact: Richard L. Reimer, Asst. Dir. CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

April 29-30—**Exercise Testing Workshop.** Tuesday-Wednesday. Univ. of Wash. Health Sciences Center, Seattle. 12 hrs. $95. Contact: Richard L. Reimer, Asst. Dir. CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

May 14-16—**Advances in Internal Medicine.** Wednesday-Friday. University Tower Hotel, Seattle. 18 hrs. $150. Contact: Richard L. Reimer, Asst. Dir. CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

May 16-17—**Washington Academy of Family Physicians Annual Meeting.** Friday-Saturday. Inn-at-the-Quay, Vancouver, Wash. 10 AAFP hrs. Contact: Walter Lapsley, Exec. Secretary, WAFP, 10003 SE Evergreen Highway, Vancouver, WA 98664.

May 16-17—**Puget Sound Academy of Otolaryngology Annual Meeting.** Friday-Saturday. Olympic Hotel, Seattle. Contact: Joseph W. Walike, MD, 1118 9th Ave., Seattle 98101. (206) 623-3700.

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May 22-23—**Pediatric Care for Family Practitioners.** Thursday-Friday. Children's Orthopedic Hospital and Medical Center, Seattle. 12 hrs. $35. Contact: William O. Robertson, MD, Director of Medical Education, Children's Orthopedic Hospital, P.O. Box 5371, Seattle 98105. (206) 634-5072.

May 25-27—**Alaska State Medical Association Annual Meeting.** Sunday-Tuesday. Glacier Bay, Alaska. Contact: Mrs. Martha L. MacDermaid, Alaska State Medical Assoc., 1135 8th Ave., Anchorage, Alaska 99501.

June 6-7—**Advances in Otolaryngology and Facial Plastic Surgery.** Friday-Saturday. Virginia Mason Medical Center Auditorium, Seattle. 9 hrs. $50. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) MA 3-3700, Ext. 470.

EFFECTIVE APPETITE DEPRESSANT with predictable pharmacological action

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Single entity amphetamine product. Each OBETROL-10 (10 mg. tablet) contains: dextroamphetamine saccharate 2.5 mg., amphetamine aspartate 2.5 mg., dextroamphetamine sulfate 2.5 mg., amphetamine sulfate 2.5 mg. OBETROL-20 (20 mg. tablets) contain twice this potency.

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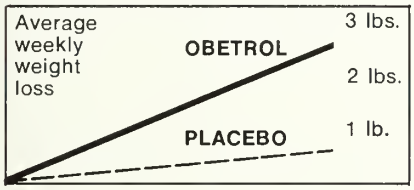
72 CASES 4 WEEKS' RESULTS



Obetrol eases the discomfort of adherence to a restricted diet in individuals who are well motivated to reduce their food intake.

Clinical studies disclose amphetamines to be the most dependable drug in a weight-reduction regimen compared to other anorexigenic agents.

Amphetamines have a significant potential for abuse. In view of their limited short-term anorectic effect and rapid development of tolerance, they should be used with extreme caution and only for limited periods of time in weight reduction programs.

Actions: Amphetamines are sympathomimetic amines with CNS stimulant activity. Peripheral actions include elevation of systolic and diastolic blood pressures and weak bronchodilator and respiratory stimulant action. The anorectic effect diminishes after a few weeks.

Indications: Exogenous obesity, as a short term (a few weeks) adjunct in a regimen of weight reduction based on caloric restriction. For patients in whom obesity is refractory to other measures.

Contraindications: Advanced arteriosclerosis, symptomatic cardiovascular disease, moderate to severe hypertension, hyperthyroidism, known hypersensitivity or idiosyncracy to the sympathomimetic amines. • Agitated states. • Patients with a history of drug abuse. • During or within 14 days following the administration of monoamine oxidase inhibitors, hypertensive crises may result.

Warnings: Tolerance to the anorectic effect usually develops within a few weeks. When this occurs, the recommended dose should not be exceeded in an attempt to increase the effect, rather, the drug should be discontinued. Amphetamines may impair the ability of the patient to engage in potentially hazardous activities such as operating machinery or driving a motor vehicle; the patient should therefore be cautioned accordingly.

Precautions: Caution is to be exercised in prescribing amphetamines for patients with even mild hypertension. Insulin requirements in diabetes mellitus may be altered in association with the use of amphetamines and the concomitant dietary regimen. Amphetamines may decrease the hypotensive effect of guanethidine. The least amount feasible should be prescribed or dispensed at one time in order to minimize the possibility of overdosage.

Adverse Reactions: *Cardiovascular:* Palpitation, tachycardia, elevation of blood pressure. Central nervous system: Overstimulation, restlessness, dizziness, insomnia, euphoria, dysphoria, tremor, headache; rarely, psychotic episodes at recommended doses. *Gastrointestinal:* Dryness of the mouth, unpleasant taste, diarrhea, other gastrointestinal disturbances. Anorexia and weight loss may occur as undesirable effects when amphetamines are used for other than the anorectic effect. *Allergic:* Urticaria. *Endocrine:* Impotence, changes in libido.

Dosage and Administration: Regardless of indication, amphetamines should be administered at the lowest effective dosage and dosage should be individually adjusted. Late evening medication should be avoided because of the resulting insomnia.

1. Narcolepsy: Usual dose 5 to 60 milligrams per day in divided doses.
2. Minimal brain dysfunction:
   a. Not recommended for children under 3 years of age.
   b. Children from 3 to 5 years of age: 2.5 milligrams daily, raised in increments of 2.5 milligrams at weekly intervals until optimal response is obtained.
   c. Children 6 years of age and older, 5 milligrams, once or twice daily, increased in increments of 5 milligrams at weekly intervals. Only in rare cases will it be necessary to exceed a total of 40 milligrams per day.
3. Obesity: Usual adult dose 5 to 30 milligrams per day in divided doses.

Overdosage: Manifestations of acute overdosage with amphetamines include restlessness, confusion, assaultiveness, hallucinations, panic states. Fatigue and depression usually follow the central stimulation. Cardiovascular effects include arrhythmias, hypertension or hypotension, and circulatory collapse. Gastrointestinal symptoms include nausea, vomiting, diarrhea, and abdominal cramps. Fatal poisoning usually terminates in convulsions and coma.

Management of acute amphetamine intoxication is largely symptomatic and includes lavage and sedation with a barbiturate. Experience with hemodialysis or peritoneal dialysis is inadequate to permit recommendations in this regard.

Availability: Supplied in bottles of 100; 500 and 1,000 tablets.

CAUTION: FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION.

January 1973

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★ **CONTINUING MEDICAL EDUCATION ACTIVITIES IN CALIFORNIA AND HAWAII; OREGON; WASHINGTON, MONTANA, ALASKA, AND IDAHO**
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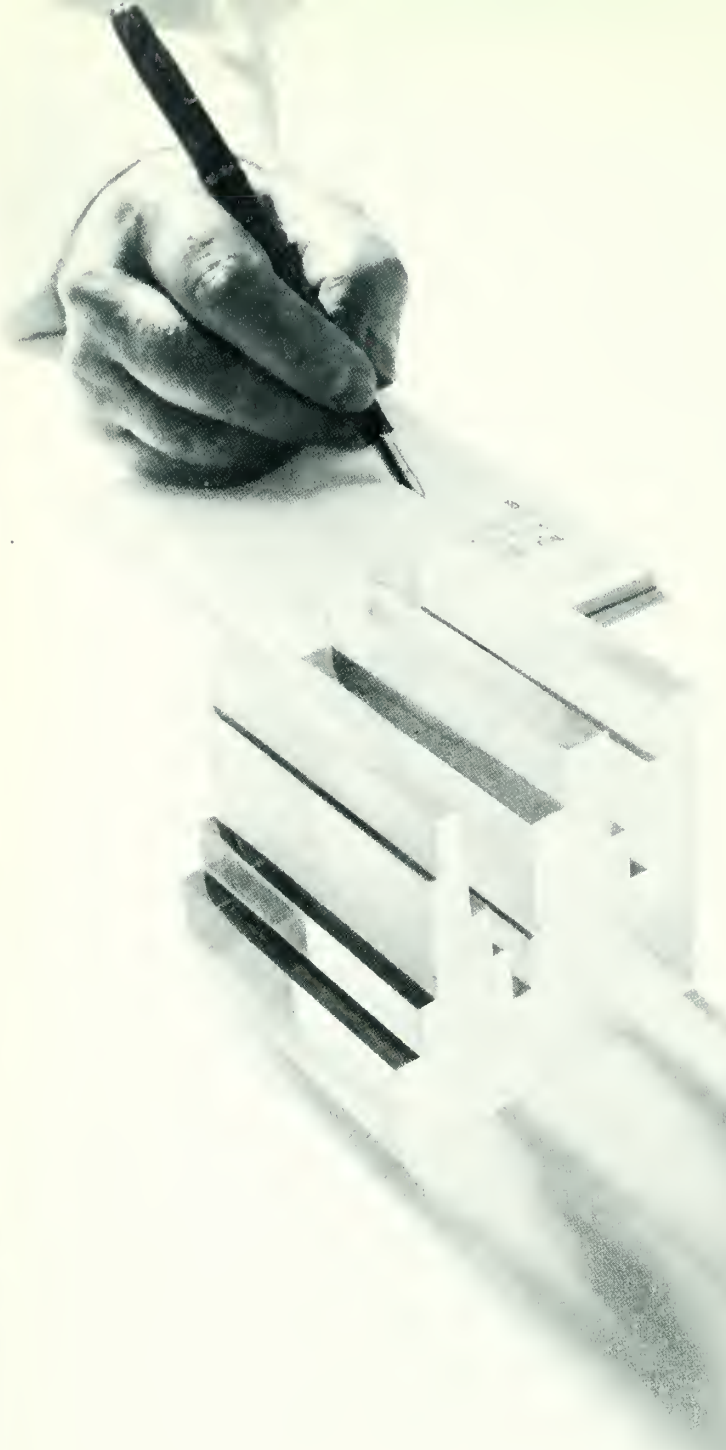

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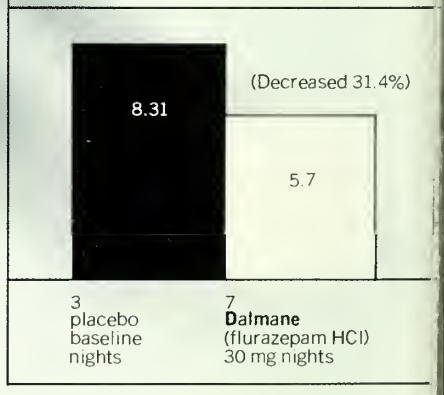

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...Dalmane (flurazepam HCl) so delivers excellent results. linically proven in sleep research boratory studies: on average, eep within 17 minutes that lasts to 8 hours.[5]

Dalmane (flurazepam HCl) relatively safe, seldom ıuses morning "hang-over"...

...and is well tolerated. The sual adult dosage is 30 mg *h.s.*, ıt with elderly and debilitated ıtients, limit the initial dose to mg to preclude oversedation, zziness or ataxia. Evaluation of ɔssible risks is advised before rescribing.

EFERENCES:

1 Karacan I, Williams RL, Smith JR: The ep laboratory in the investigation of sleep d sleep disturbances. Scientific exhibit at 124th annual meeting of the American ychiatric Association, Washington DC, ıy 3-7, 1971

2 Frost JD Jr: A system for automatically alyzing sleep. Scientific exhibit at th annual Clinical Convention of the nerican Medical Association, Boston, v 29-Dec 2, 1970; and at the 42nd annual entific meeting of the Aerospace Medical sociation, Houston, Apr 26-29, 1971

3 Vogel GW: Data on file, Medical Depart-nt, Hoffmann-La Roche Inc., Nutley NJ

4 Dement WC: Data on file, Medical Depart-nt, Hoffmann-La Roche Inc., Nutley NJ

5 Data on file, Medical Department, ffmann-La Roche Inc., Nutley NJ

fore prescribing Dalmane (flurazepam Cl), please consult complete product ormation, a summary of which follows:

lications: Effective in all types of insomnia aracterized by difficulty in falling asleep, quent nocturnal awakenings and/or early rning awakening; in patients with recurring omnia or poor sleeping habits; and in ute or chronic medical situations requiring tful sleep. Since insomnia is often transient d intermittent, prolonged administration is nerally not necessary or recommended.

ntraindications: Known hypersensitivity flurazepam HCl.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. Caution against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Use in women who are or may become pregnant only when potential benefits have been weighed against possible hazards. Not recommended for use in persons under 15 years of age. Though physical and psychological dependence have not been reported on recommended doses, use caution in administering to addiction-prone individuals or those who might increase dosage.

Precautions: In elderly and debilitated, initial dosage should be limited to 15 mg to preclude oversedation, dizziness and/or ataxia. If combined with other drugs having hypnotic or CNS-depressant effects, consider potential additive effects. Employ usual precautions in patients who are severely depressed, or with latent depression or suicidal tendencies. Periodic blood counts and liver and kidney function tests are advised during repeated therapy. Observe usual precautions in presence of impaired renal or hepatic function.

Adverse Reactions: Dizziness, drowsiness, lightheadedness, staggering, ataxia and falling have occurred, particularly in elderly or debilitated patients. Severe sedation, lethargy, disorientation and coma, probably indicative of drug intolerance or overdosage, have been reported. Also reported were headache, heartburn, upset stomach, nausea, vomiting, diarrhea, constipation, GI pain, nervousness, talkativeness, apprehension, irritability, weakness, palpitations, chest pains, body and joint pains and GU complaints. There have also been rare occurrences of sweating, flushes, difficulty in focusing, blurred vision, burning eyes, faintness, hypotension, shortness of breath, pruritus, skin rash, dry mouth, bitter taste, excessive salivation, anorexia, euphoria, depression, slurred speech, confusion, restlessness, hallucinations, and elevated SGOT, SGPT, total and direct bilirubins and alkaline phosphatase. Paradoxical reactions, *e.g.*, excitement, stimulation and hyperactivity, have also been reported in rare instances.

Dosage: Individualize for maximum beneficial effect. *Adults:* 30 mg usual dosage; 15 mg may suffice in some patients. *Elderly or debilitated patients:* 15 mg initially until response is determined.

Supplied: Capsules containing 15 mg or 30 mg flurazepam HCl.

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(flurazepam HCl)

One 30-mg capsule *h.s.*— usual adult dosage (15 mg may suffice in some patients).
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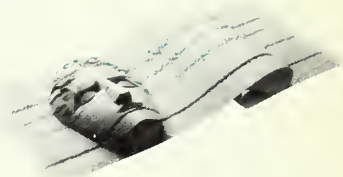

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- **sleep with fewer nighttime awakenings**
- **sleep within 17 minutes, on average**
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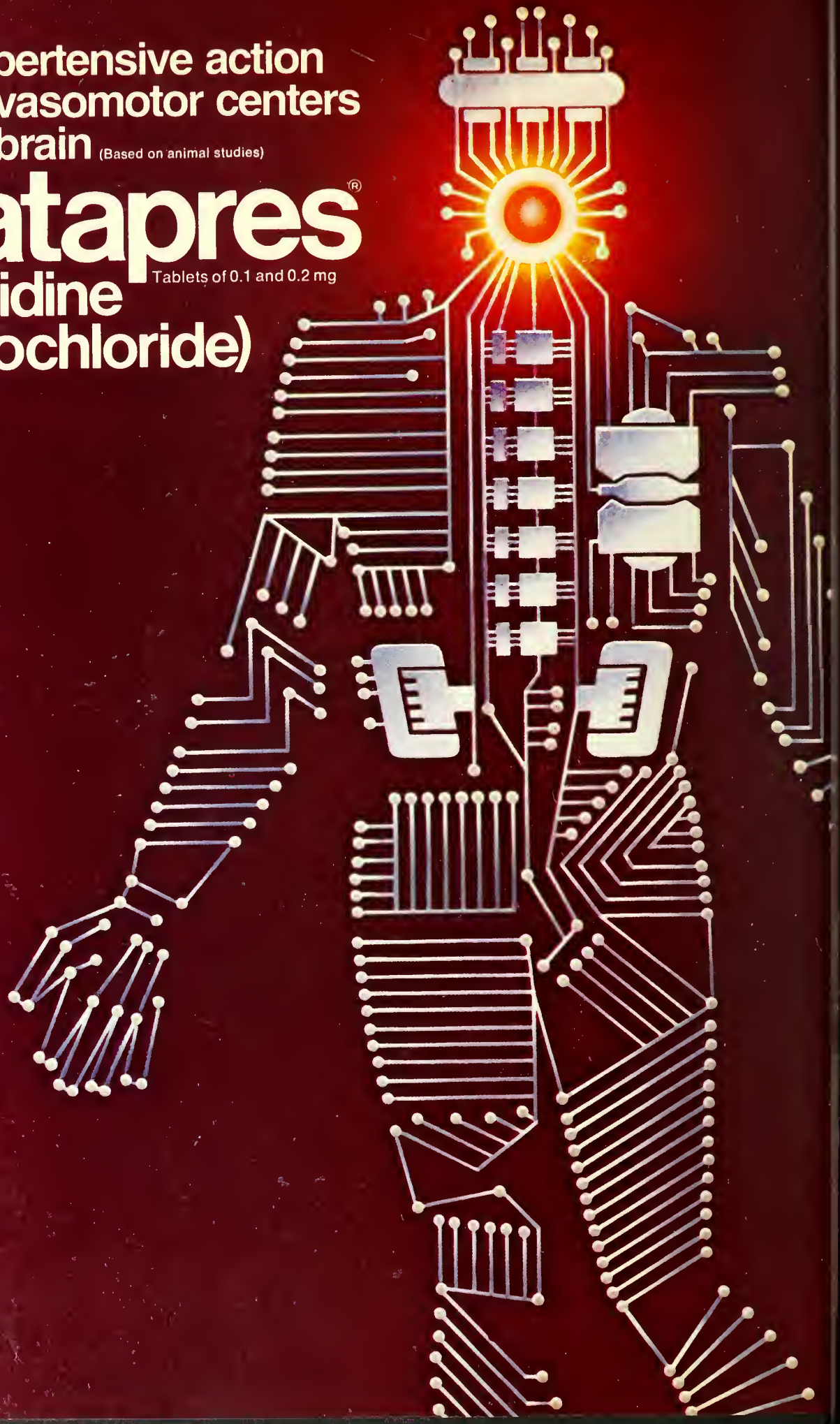
(clonidine
hydrochloride)



Central action

Catapres appears to lower blood pressure through central alpha-adrenergic stimulation, as shown in animal studies. This results in diminution—but not blocking—of sympathetic outflow from cardioaccelerator and vasoconstrictor centers in the medulla.

Not a "depleter", "blocker", "inhibitor" or "false transmitter"

Not a rauwolfia

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Effective in hypertension, mild to severe

Mild and infrequent orthostatic hypotension

Normal hemodynamic responses to exercise are unaffected

Renal blood flow and glomerular filtration rate essentially unchanged

Mild to moderate potency

The most common side effects are dry mouth, drowsiness and sedation. These generally tend to diminish with continued therapy. Other potential adverse reactions are listed in the Brief Summary.

Catapres® (clonidine hydrochloride)
Tablets of 0.1 mg and 0.2 mg

Indication: The drug is indicated in the treatment of hypertension. As an antihypertensive drug, Catapres (clonidine hydrochloride) is mild to moderate in potency. It may be employed in a general treatment program with a diuretic and/or other antihypertensive agents as needed for proper patient response.

Warnings: Tolerance may develop in some patients necessitating a reevaluation of therapy.
Usage in Pregnancy: In view of embryotoxic findings in animals, and since information on possible adverse effects in pregnant women is limited to uncontrolled clinical data, the drug is not recommended in women who are or may become pregnant unless the potential benefits outweigh the potential risk to mother and fetus.
Usage in Children: No clinical experience is available with the use of Catapres (clonidine hydrochloride) in children.

Precautions: When discontinuing Catapres (clonidine hydrochloride), reduce the dose gradually over 2 to 4 days to avoid a possible rapid rise in blood pressure and associated subjective symptoms such as nervousness, agitation, and headache. Patients should be instructed not to discontinue therapy without consulting their physician. Rare instances of hypertensive encephalopathy and death have been recorded after cessation of clonidine hydrochloride therapy. A causal relationship has not been established in these cases. It has been demonstrated that an excessive rise in blood pressure, should it occur, can be reversed by resumption of clonidine hydrochloride therapy or by intravenous phentolamine. Patients who engage in potentially hazardous activities, such as operating machinery or driving should be advised of the sedative effect. This drug may enhance the CNS-depressive effects of alcohol, barbiturates and other sedatives. Like any other agent lowering blood pressure, clonidine hydrochloride should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease or chronic renal failure.

As an integral part of their overall long-term care, patients treated with Catapres (clonidine hydrochloride) should receive periodic eye examinations. While, except for some dryness of the eyes, no drug-related abnormal ophthalmologic findings have been recorded with Catapres, in several studies the drug produced a dose-dependent increase in the incidence and severity of spontaneously occurring retinal degeneration in albino rats treated for 6 months or longer.

Adverse Reactions: The most common reactions are dry mouth, drowsiness and sedation. Constipation, dizziness, headache, and fatigue have been reported. Generally these effects tend to diminish with continued therapy. The following reactions have been associated with the drug, some of them rarely. (In some instances an exact causal relationship has not been established). These include: Anorexia, malaise, nausea, vomiting, parotid pain, mild transient abnormalities in liver function tests; one report of possible drug-induced hepatitis without icterus and hyperbilirubinemia in a patient receiving clonidine hydrochloride, chlorthalidone and papaverine hydrochloride.

Weight gain, transient elevation of blood glucose, or serum creatine phosphokinase; congestive heart failure, Raynaud's phenomenon; vivid dreams or nightmares, insomnia, other behavioral changes, nervousness, restlessness, anxiety and mental depression. Also rash, angioneurotic edema, hives, urticaria, thinning of the hair, pruritus not associated with a rash, impotence, urinary retention, increased sensitivity to alcohol, dryness, itching or burning of the eyes, dryness of the nasal mucosa, pallor, gynecomastia, weakly positive Coombs' test, asymptomatic electrocardiographic abnormalities manifested as Wenckebach period or ventricular trigeminy.

Overdosage: Profound hypotension, weakness, somnolence, diminished or absent reflexes and vomiting followed the accidental ingestion of Catapres (clonidine hydrochloride) by several children from 19 months to 5 years of age. Gastric lavage and administration of an analeptic and vasopressor led to complete recovery within 24 hours. Tolazoline in intravenous doses of 10 mg at 30-minute intervals usually abolishes all effects of Catapres (clonidine hydrochloride) overdosage.

How Supplied: Catapres, brand of clonidine hydrochloride, is available as 0.1 mg (tan) and 0.2 mg (orange) oval, single-scored tablets in bottles of 100.

For complete details, please see full prescribing information.

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What to do when your patient feels robbed of milk, cream and saturated fat.

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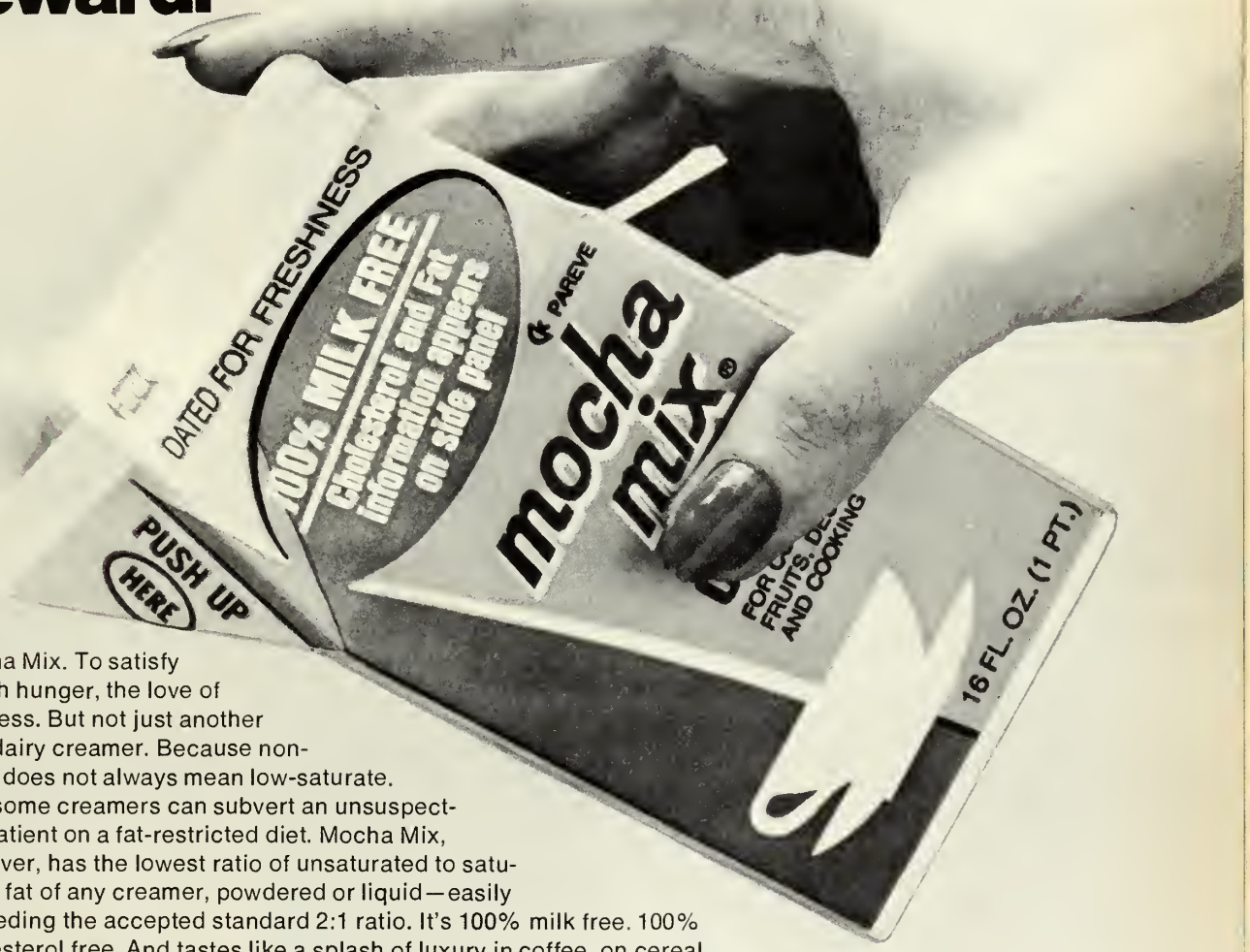

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Calories	40
Protein	0 grams
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Polyunsaturated Fat	1 gram
Saturated Fat	0 grams
Cholesterol	0

(Percentage of U.S. Recommended Daily Allowances (U.S., RDA)*

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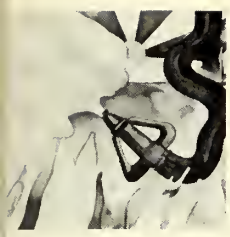

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Varnings: Patients with severe cardiac lisease should be given this medication vith caution. Fever and possibly heat stroke nay occur due to anhidrosis.

Overdosage may cause a curare-like action, vith loss of voluntary muscle control. For such patients prompt and continuing rtificial respiration should be applied until he drug effect has been exhausted.

Diarrhea in an ileostomy patient may indicate bstruction, and this possibility should be con-idered before administering Pro-Banthīne.

Precautions: Since varying degrees of urinary esitancy may be evidenced by elderly males vith prostatic hypertrophy, such patients hould be advised to micturate at the time f taking the medication.

Overdosage should be avoided in patients everely ill with ulcerative colitis.

Adverse Reactions: Varying degrees of rying of salivary secretions may occur as vell as mydriasis and blurred vision. In addition the following adverse reactions have een reported: nervousness, drowsiness, izziness, insomnia, headache, loss of the ense of taste, nausea, vomiting, constipation, mpotence and allergic dermatitis.

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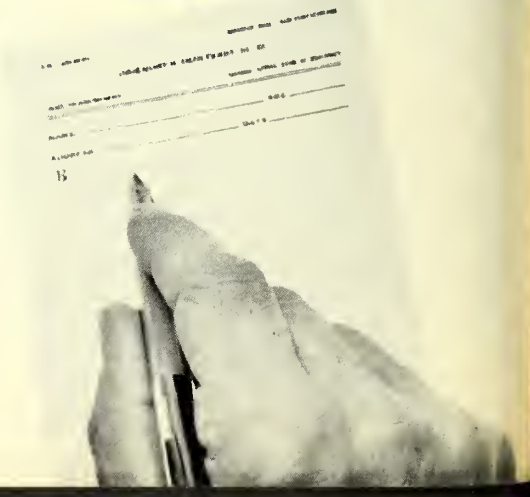
Bioequivalence



the weight of scientific opinion:

If the pharmacist substituted a chemically equivalent drug for the one you have specified for your patient—could you be certain of that product's safety and effectiveness simply because the chemical content was the same?

Definitely not, unless bioequivalence tests and other quality assurance checks had been conducted. The pharmaceutical industry and many scientists have maintained this position for years, but others have questioned it. Now the Office of Technology Assessment of the Congress of the United States has reported on the issue in its Drug Bioequivalence Study.*

Here are a few definitive statements in the O.T.A. report:

"...the problem of bioinequivalency in chemically equivalent products is a real one. Since the studies in which lack of bioequivalence was demonstrated involved marketed products that met current compendial standards, these documented instances constitute unequivocal evidence that neither the present standards for testing the finished product nor the specifications for materials, manufacturing process, and controls are adequate to ensure that ostensibly equivalent drug products are, in fact, equivalent in bioavailability.

"While these therapeutic failures resulting from problems of bioavailability were recognized and well documented, it is entirely possible that other therapeutic failures and/or instances of toxicity that had a similar basis have escaped attention."

The Pharmaceutical Manufacturers Association supports federal legislative amendments that would require manufacturers of duplicate prescription pharmaceutical products, subject to new drug procedures, to document:

(a) chemical equivalence; and (b) biological equivalence, where bioavailability test methods have been validated as a reliable means of assuring clinical equivalence; or (c) where such validation is not possible, therapeutic equivalence.

In addition, the PMA supports federal legislation that would require certification of all manufacturers of prescription products before they could start in business, annual inspections and certification thereafter, and strict adherence to FDA regulations on good manufacturing practices.

The overall quality of the United States drug supply is excellent. But only a total quality assurance program, envisaged in these and other policy positions adopted by the PMA Board of Directors in 1974, can bring about acceptable levels of performance by all prescription drug manufacturers and thereby assure the integrity of your prescription...

P·M·A

Pharmaceutical Manufacturers Association
1155 Fifteenth Street, N.W.
Washington, D.C. 20005

*Copies of the complete report on Drug Bioequivalence may be obtained from the Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402.

protecting the integrity of your prescription

Before prescribing, see complete prescribing information in SK&F literature or *PDR*. The following is a brief summary.

Indications: Edema associated with congestive heart failure, cirrhosis of the liver, the nephrotic syndrome; steroid-induced and idiopathic edema; edema resistant to other diuretic therapy. Also, mild to moderate hypertension.

Contraindications: Pre-existing elevated serum potassium. Hypersensitivity to either component. Continued use in progressive renal or hepatic dysfunction or developing hyperkalemia.

Warnings: **Do not use dietary potassium supplements or potassium salts unless hypokalemia develops or dietary potassium intake is markedly impaired.** Enteric-coated potassium salts may cause small bowel stenosis with or without ulceration. Hyperkalemia (>5.4 mEq/L) has been reported in 4% of patients under 60 years, in 12% of patients over 60 years, and in less than 8% of patients overall. Rarely, cases have been associated with cardiac irregularities. Accordingly, **check serum potassium during therapy, particularly in patients with suspected or confirmed renal insufficiency (e.g., elderly or diabetics). If hyperkalemia develops, substitute a thiazide alone. If spironolactone is used concomitantly with 'Dyazide', check serum potassium frequently**—both can cause potassium retention and sometimes hyperkalemia. Two deaths have been reported in patients on such combined therapy (in one, recommended dosage was exceeded; in the other, serum electrolytes were not properly monitored). Observe patients on 'Dyazide' regularly for possible blood dyscrasias, liver damage or other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving Dyrenium (triamterene, SK&F). Rarely, leukopenia, thrombocytopenia, agranulocytosis, and aplastic anemia have been reported with the thiazides. Watch for signs of impending coma in acutely ill cirrhotics. Thiazides are reported to cross the placental barrier and appear in breast milk. This may result in fetal or neonatal hyperbilirubinemia, thrombocytopenia, altered carbohydrate metabolism and possibly other adverse reactions that have occurred in the adult. When used during pregnancy or in women who might bear children, weigh potential benefits against possible hazards to fetus.

Precautions: Do periodic serum electrolyte and BUN determinations. Do periodic hematologic studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in postsympathectomy patients. The following may occur: hyperuricemia and gout, reversible nitrogen retention, decreasing alkali reserve with possible metabolic acidosis, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), digitalis intoxication (in hypokalemia). Use cautiously in surgical patients. Concomitant use with antihypertensive agents may result in an additive hypotensive effect.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis; rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting (may indicate electrolyte imbalance), diarrhea, constipation, other gastrointestinal disturbances. Rarely, necrotizing vasculitis, paresthesias, icterus, pancreatitis, and xanthopsia have occurred with thiazides alone.

Supplied: Bottles of 100 capsules; in Single Unit Packages of 100 (intended for institutional use only).

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The Four Food Groups—milk, meat, vegetables and fruits, breads and cereals—a practical guide to good nutrition.

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OB/GYN RESIDENCY—Second year available July 1, 1975. Fully approved program. All qualified applicants urged to apply. Valid California license must be in hand. Salary $15,432 annually, plus fringe benefits. Contact Dr. Leroy Smale, Chairman, Kern General Hospital, 1830 Flower Street, Bakersfield, CA 93305.

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PHYSICIAN—Preferably board certified in internal medicine or general practice for internal medicine or ambulatory care services. Pending university affiliation for internal medicine residency. Fully equipped and staffed hospital, excellent laboratory and library services, fine consultation in a magnificient western setting with all the advantages of outdoor living. Salary range: $28-$36,000. Forty-hour week. Excellent employment benefits with 30 days annual vacation and the best sick leave, retirement, health and life insurance available. An Equal Opportunity Employer. Contact: Frank R. Mohs, MD, Chief of Staff, VA Hospital, Boise, Idaho 83702, or call (208) 342-3681.

MILLS COLLEGE, OAKLAND, CALIFORNIA, a College for women, is seeking a qualified physician to assume full responsibility for primary health care; and be part of a broader health team involved in an innovative program to develop new patterns for health of the Mills community. Please send letter of application and vita to Office of the President, Mills College, Oakland, CA 94613.

PULMONARY DISEASE PHYSICIAN, certified, to associate with a Cardiologist in Orange County. Send curriculum vitae to: E. C. Gaulden, MD, 17541 Irvine Blvd., Tustin, CA, or call (714) 838-2655.

(Continued on Page 16)

PHYSICIAN

For public hospital practice in semi-rurel area of So. Calif. Need doctors for out-petient clinic or medical wards. Excellent civil service benefits and retirement plan. Health insurance and malpractice paid. Salary range: G.P.'s $2,228-$2,920. Specialists: $2,487-$3,816. Calif. license end valid BNDD required. Contact: Dr. Harry Glenchur, MD, Medical Director—Mira Loma Hospital, 44900 N. 60th St. West, Lancaster, CA (805) 948-8581.

Board eligible or certified physiatrist for university affiliated medical center. Clinical teaching and research opportunity in a mejor rehabilitation center including Federal Regional Spinal Cord Injury Program. Unique head injury program, burn rehabilitation, cardiac rehabilitation, general rehabilitation, and electrodiagnosis. Undergraduate teaching end residency training programs. 70 acute rehab beds in a 625 bed institution in the San Francisco Bay Area. Apply with curriculum vitae to:

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EXCELLENT IMMEDIATE OPPORTUNITY for Pulmonary Internist to join Board Certified Pulmonary Specialist in San Diego, California. Private practice includes office care, hospital consultations, and medical direction of Respiratory Therapy-Pulmonary Function Departments. Reply with curriculum vitae to: Jerry E. Fein, MD, 6355 Ridge Manor Ave, San Diego, CA 92120.

OB-GYN: For Neighborhood Health Center clinic near San Jose, California. Potential for teeching opportunities and staff privileges at two major academic medical centers. Spanish speaking ability helpful but not necessary. Practice in a suburban and semi-rural area with beautiful weather and excellent recreational and vacation facilities. Salary: Negotiable, excellent fringe benefits. Send curriculum vitae to Richard Ross, MD, Medical Director, 1621 Gold St., Alviso, CA 95002.

DIRECTOR, Primary Care Program, St. Vincent Hospital & Medical Center, Portland, Oregon. Serves rapidly growing suburban community. Assume overall responsibility for new Family Medical Care Unit. Assist in formulation of long-range plans for primary care program. Requires board eligibility in Family Practice or Internal Medicine, experience in primary care practice, plus teaching interest and capability. Reply Box 9410, The Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

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Doctor, when you complete your training, what are your goals? (1) Economic security? (2) Provide your expertise where it is needed and appreciated? (3) To practice in an area that assures an abundant life for you and your family? (4) Continuing education and stimulation? If you answered yes to all of the above questions, then you are precisely the alert, perceptive Internist or Pediatrician we are looking for to associate with a nine-man, multi-specialty group. Send résumé at once to:

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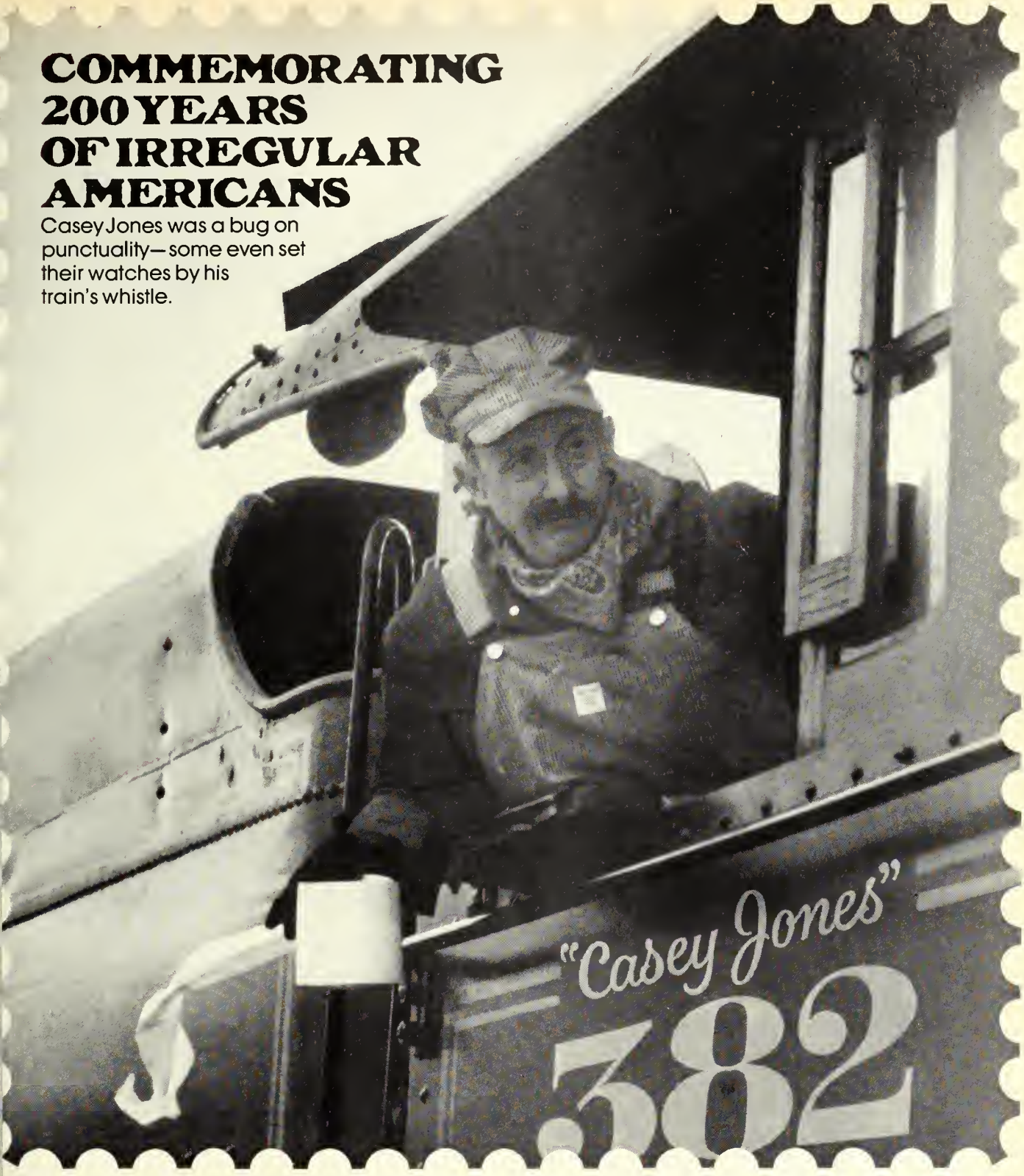

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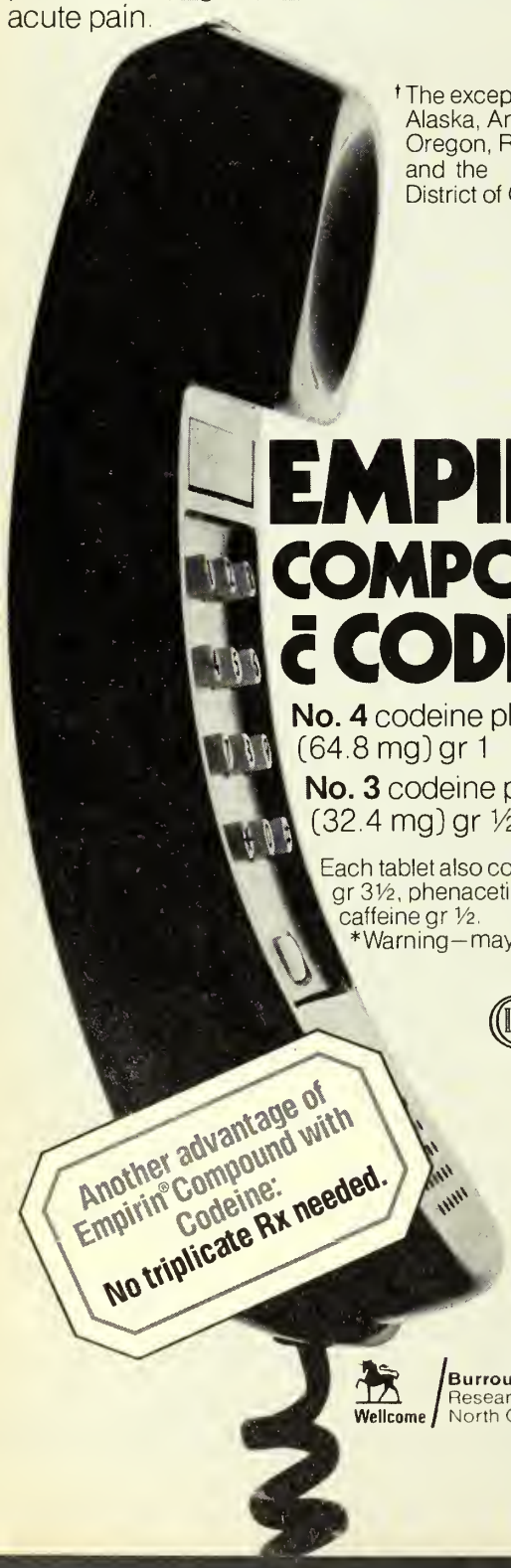

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PROLOID® (thyroglobulin)

Caution: Federal law prohibits dispensing without prescription.

Description. Proloid (thyroglobulin) is obtained from a purified extract of frozen hog thyroid. It contains the known calorigenically active components, Sodium Levothyroxine (T_4) and Sodium Liothyronine (T_3). Proloid (thyroglobulin) conforms to the primary USP specifications for desiccated thyroid—for iodine based on chemical assay—and is also biologically assayed and standardized in animals.

Chromatographic analysis to standardize the Sodium Levothyroxine and Sodium Liothyronine content of Proloid (thyroglobulin) is routinely employed.

The ratio of T_4 and T_3 in Proloid (thyroglobulin) is approximately 2.5 to 1.

Proloid (thyroglobulin) is stable when stored at usual room temperature.

Indications. Proloid (thyroglobulin) is thyroid replacement therapy for conditions of inadequate endogenous thyroid production: e.g., cretinism and myxedema. Replacement therapy will be effective only in manifestations of hypothyroidism.

In simple (nontoxic) goiter, Proloid (thyroglobulin) may be tried therapeutically, in nonemergency situations, in an attempt to reduce the size of such goiters.

Contraindication. Thyroid preparations are contraindicated in the presence of uncorrected adrenal insufficiency.

Warnings. Thyroglobulin should not be used in the presence of cardiovascular disease unless thyroid-replacement therapy is clearly indicated. If the latter exists, low doses should be instituted beginning at 0.5 to 1.0 grain (32 to 64 mg) and increased by the same amount in increments at two-week intervals. This demands careful clinical judgment.

Morphologic hypogonadism and nephroses should be ruled out before the drug is administered. If hypopituitarism is present, the adrenal deficiency must be corrected prior to starting the drug.

Myxedematous patients are very sensitive to thyroid and dosage should be started at a very low level and increased gradually.

Precaution. As with all thyroid preparations this drug will alter results of thyroid function tests.

Adverse Reactions. Overdosage or too rapid increase in dosage may result in signs and symptoms of hyperthyroidism, such as menstrual irregularities, nervousness, cardiac arrhythmias, and angina pectoris.

Dosage and Administration. Optimal dosage is usually determined by the patient's clinical response. Confirmatory tests include BMR, $T_3{}^{131}I$ resin sponge uptake, $T_3{}^{131}I$ red cell uptake, Thyro Binding Index (TBI), and Achilles Tendon Reflex Test. Clinical experience has shown that a normal PBI (3.5-8 mcg/100 ml) will be obtained in patients made clinically euthyroid when the content of T_4 and T_3 is adequate. Dosage should be started in small amounts and increased gradually with increments at intervals of one to two weeks. Usual maintenance dose is 0.5 to 3.0 grains (32 to 190 mg) daily.

Instructions for Use. The following conversion table lists the approximate equivalents of other thyroid preparations to Proloid (thyroglobulin) when changing medication from desiccated thyroid, T_4 (sodium levothyroxine), T_3 (sodium liothyronine), or T_4/T_3 (liotrix).

CONVERSION TABLE

Dose of Proloid (thyroglobulin)	Dose of Desiccated Thyroid	Dose of T_4 (sodium levothyroxine)	Dose of T_3 (sodium liothyronine)	Dose of liotrix (T_4/T_3)
1 grain	1 grain	0.1 mg	25 mcg	#1 (60 mcg/15 mcg)
2 grains	2 grains	0.2 mg	50 mcg	#2 (120 mcg/30 mcg)
3 grains	3 grains	0.3 mg	75 mcg	#3 (180 mcg/45 mcg)
4 grains	4 grains	0.4 mg	100 mcg	
5 grains	5 grains	0.5 mg	125 mcg	

In changing from Thyroid USP to Proloid (thyroglobulin), substitute the equivalent dose of Proloid (thyroglobulin). Each patient may still require fine adjustment of dosage because the equivalents are only estimates.

Overdosage Symptoms. Headache, instability, nervousness, sweating, tachycardia, with unusual bowel motility. Angina pectoris or congestive heart failure may be induced or aggravated. Shock may develop. Massive overdosage may result in symptoms resembling thyroid storm. Chronic excessive dosage will produce the signs and symptoms of hyperthyroidism.

(Treatment: In shock, supportive measures should be utilized. Treatment of unrecognized adrenal insufficiency should be considered.)

Supplied. ¼ grain tablets in bottles of 100 (N 0047-0250-51) and 1000 (N 0047-0250-60); ½ grain tablets in bottles of 100 (N 0047-0251-51) and 1000 (N 0047-0251-60); scored 1 grain tablets in bottles of 100 (N 0047-0252-51) and 1000 (N 0047-0252-60); 1½ grain tablets in bottles of 100 (N 0047-0253-51) and 1000 (N 0047-0253-60); scored 2 grain tablets in bottles of 100 (N 0047-0257-51); 3 grain tablets in bottles of 100 (N 0047-0254-51) and 1000 (N 0047-0254-60); scored 5 grain tablets in bottles of 100 (N 0047-0255-51) and 1000 (N 0047-0255-60). Full information is available on request. P-GP-51 4/c

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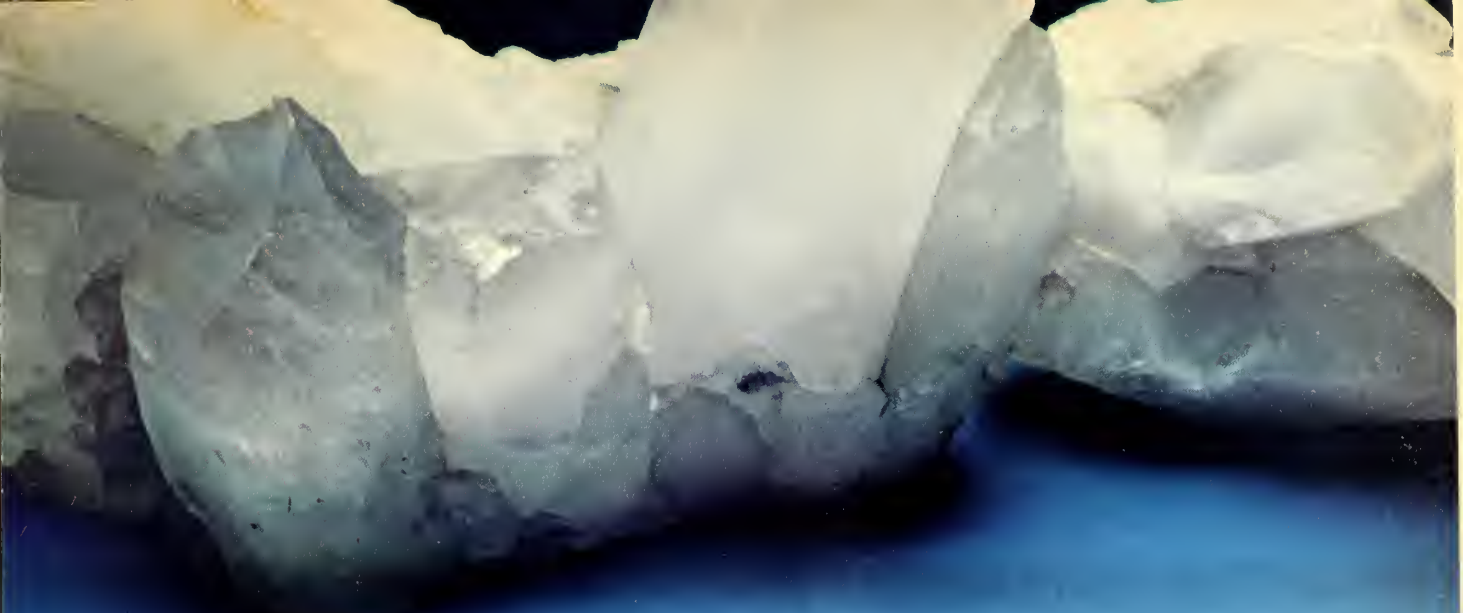

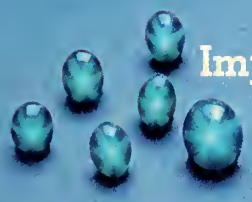

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Potency undiminished for up to 4 years under proper storage conditions.

It all adds up to natural thyroid with the added improvements of man.

Please see adjoining column for brief summary of prescribing information.

(Continued from Page 12)

PHYSICIANS WANTED

51-YEAR OLD PRACTITIONER engaged in the successful practice of Internal Medicine with 50 percent Cardiology in a solid Southern California community, desires long-term association with mature, energetic, Board Certified general Internist with quality credentials, who is desirous of an immediate opportunity in an incorporated practice with qualified retirement programs. Immediate opportunity for substantial earnings, coupled with a long-term opportunity for acquisition of the practice. Write: Box No. 9409, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

STAFF PSYCHIATRIST—Community based total health care program. Team approach is used to provide full range of direct and indirect services to rural and urban communities. Located in the Central Valley close to San Francisco, Los Angeles, ocean and the mountains. Contact: J. Frank James, MD, 515 South Cedar Ave., Fresno, CA 93702, (209) 488-3747.

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SITUATIONS WANTED

FAMILY PRACTITIONER, 58, wishes part-time work, 2 to 8 months/year; or share practice in an FP's location. Prefer Calif. Richard Ricklefs, MD, Box 1330 Fairbanks, AK 99701; (907) 452-5717.

CARDIOLOGIST, 37, Board Certified, fully trained in invasive and non-invasive procedures. Prefer West Coast hospital based practice, academic or private. Write for C.V., Box 9407, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

AVAILABLE ANESTHETIST on free lance basis for office come-and-go procedures. San Francisco Area. Call: Eula Walters, CRNA, (415) 391-3339.

PATHOLOGIST—Seeking director or associate position in Calif. Board certified in AP-CP. Calif. license. Ten years experience, director of laboratory in small hospitals. Available March, 1975. Reply Box 9412, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

PRACTICES FOR SALE

OPHTHALMOLOGY practice for sale. Leaving for academic position. Extremely lucrative—heavy surgical. New Mexico. Reply box No. 9411, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

REDDING, CALIFORNIA—Fully equipped and stocked office available due to recent physical disability retirement. Excellent opportunity for General Practitioner. Long established practice. Open Staff Hospitals. Howard A. Wells, MD, 1434 East St., Redding, CA 96001, (916) 243-1414.

MEDICAL EQUIPMENT FOR SALE

UNIMETER 250 Bio-Dynamics No. 708—Sell $300, BMI Blood Analyzer No. 587—Sell $225, Call (408) 262-5910 or (408) 263-3195.

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FOR RENT: The newest and largest professional building in the South San Diego community of Imperial Beach, suites available can be customized to suit tenant. This is excellent opportunity for pediatrics, gynecology, dermatology, ophthalmology, general surgery, general practice, internal medicine and psychiatry. Photos and particulars available upon request from John E. Geis, DDS, 218 Palm Ave., Imperial Beach, CA 92032; office (714) 424-3931.

LEASE 1200 SQ. FT. SUITE. Four treatment rooms with or without equipment. G.P. leaving for health reasons; San Mateo area; (415) 341-8440.

RADIOLOGY LABORATORY—Suburban office 45 minutes from downtown San Francisco. Fully equipped for general radiology. Satellite office —no longer needed. Going practice. Prompt possession. (415) 781-6863. Cash or terms.

HUNTINGTON BEACH—50¢/square foot. New four suite professional building ready for immediate occupancy. 150 feet from the entrance of the Huntington Intercommunity Hospital. Contact Dr. Arnold Angelici, 8101 Newman Ave., Huntington Beach, CA 92647; phone (714) 842-2549.

BEAUTIFUL NEW 2-STORY A.C. PROFESSIONAL BUILDING with x-ray, lab and pharmacy on premises. Next door to hospital, excellent parking. Leases available on suites 1,100 to 1,400 sq ft at 67¢ sq ft. Call (714) 646-9326 or (714) 774-0601. Costa Mesa, So. California.

SEMI-RETIRE IN RESORT COMMUNITY—Take over satellite office manned by a competent Medex near Ocean Shores, WA. Presently I attend ½ day per week; two or three ½ days would be better. Best background would be GP, GYN, or general surgeon. Let Medex make the night calls and continue pesent primary care with physician backup. Office has basic lab (Medex is registered med tech), extremity x-ray, and 1½ years of operation to prove its viability. Direct inquiries to: C. A. Pollock, MD, 1812 Summer, Aberdeen, WA 98520.

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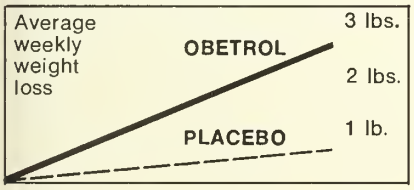

Obetrol eases the discomfort of adherence to a restricted diet in individuals who are well motivated to reduce their food intake.

Clinical studies disclose amphetamines to be the most dependable drug in a weight-reduction regimen compared to other anorexigenic agents.

Amphetamines have a significant potential for abuse. In view of their limited short-term anorectic effect and rapid development of tolerance, they should be used with extreme caution and only for limited periods of time in weight reduction programs.

Actions: Amphetamines are sympathomimetic amines with CNS stimulant activity. Peripheral actions include elevation of systolic and diastolic blood pressures and weak bronchodilator and respiratory stimulant action. The anorectic effect diminishes after a few weeks.

Indications: Exogenous obesity, as a short term (a few weeks) adjunct in a regimen of weight reduction based on caloric restriction. For patients in whom obesity is refractory to other measures.

Contraindications: Advanced arteriosclerosis, symptomatic cardiovascular disease, moderate to severe hypertension, hyperthyroidism, known hypersensitivity or idiosyncracy to the sympathomimetic amines. • Agitated states. • Patients with a history of drug abuse. • During or within 14 days following the administration of monoamine oxidase inhibitors, hypertensive crises may result.

Warnings: Tolerance to the anorectic effect usually develops within a few weeks. When this occurs, the recommended dose should not be exceeded in an attempt to increase the effect, rather, the drug should be discontinued. Amphetamines may impair the ability of the patient to engage in potentially hazardous activities such as operating machinery or driving a motor vehicle; the patient should therefore be cautioned accordingly.

Precautions: Caution is to be exercised in prescribing amphetamines for patients with even mild hypertension. Insulin requirements in diabetes mellitus may be altered in association with the use of amphetamines and the concomitant dietary regimen. Amphetamines may decrease the hypotensive effect of guanethidine. The least amount feasible should be prescribed or dispensed at one time in order to minimize the possibility of overdosage.

Adverse Reactions: *Cardiovascular:* Palpitation, tachycardia, elevation of blood pressure. Central nervous system: Overstimulation, restlessness, dizziness, insomnia, euphoria, dysphoria, tremor, headache; rarely, psychotic episodes at recommended doses. *Gastrointestinal:* Dryness of the mouth, unpleasant taste, diarrhea, other gastrointestinal disturbances. Anorexia and weight loss may occur as undesirable effects when amphetamines are used for other than the anorectic effect. *Allergic:* Urticaria. *Endocrine:* Impotence, changes in libido.

Dosage and Administration: Regardless of indication, amphetamines should be administered at the lowest effective dosage and dosage should be individually adjusted. Late evening medication should be avoided because of the resulting insomnia.

1. Narcolepsy: Usual dose 5 to 60 milligrams per day in divided doses.
2. Minimal brain dysfunction:
   a. Not recommended for children under 3 years of age.
   b. Children from 3 to 5 years of age: 2.5 milligrams daily, raised in increments of 2.5 milligrams at weekly intervals until optimal response is obtained.
   c. Children 6 years of age and older, 5 milligrams, once or twice daily, increased in increments of 5 milligrams at weekly intervals. Only in rare cases will it be necessary to exceed a total of 40 milligrams per day.
3. Obesity: Usual adult dose 5 to 30 milligrams per day in divided doses.

Overdosage: Manifestations of acute overdosage with amphetamines include restlessness, confusion, assaultiveness, hallucinations, panic states. Fatigue and depression usually follow the central stimulation. Cardiovascular effects include arrhythmias, hypertension or hypotension, and circulatory collapse. Gastrointestinal symptoms include nausea, vomiting, diarrhea, and abdominal cramps. Fatal poisoning usually terminates in convulsions and coma.

Management of acute amphetamine intoxication is largely symptomatic and includes lavage and sedation with a barbiturate. Experience with hemodialysis or peritoneal dialysis is inadequate to permit recommendations in this regard.

Availability: Supplied in bottles of 100; 500 and 1,000 tablets.

CAUTION: FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION.

January 1973

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IN GONORRHEA

INJECTION

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(STERILE PROCAINE PENICILLIN G SUSPENSION) WYETH

Gonorrhea, according to the national Center for Disease Control, is, if the parenteral route is chosen, most effectively treated with aqueous procaine penicillin G. In uncomplicated cases, administration of 4.8 million units together with 1 gram oral probenecid, given at least 30 minutes prior to injection, is recommended.

Indications: In treatment of moderately severe infections due to penicillin G-sensitive microorganisms sensitive to the low and persistent serum levels common to this particular dosage form. Therapy should be guided by bacteriological studies (including sensitivity tests) and by clinical response.

NOTE: When high sustained serum levels are required use aqueous penicillin G, IM or IV.

The following infection will usually respond to adequate dosages of intramuscular procaine penicillin G.—*N. gonorrhoeae:* acute and chronic (without bacteremia).

For deep intramuscular injection only.

Contraindications: Previous hypersensitivity reaction to any penicillin.

Warnings: Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy.

Serious anaphylactoid reactions require immediate emergency treatment with epinephrine. Oxygen and intravenous corticosteroids should also be administered as indicated.

Although anaphylaxis is more frequent following parenteral therapy it has occurred in patients on oral penicillins. These reactions are more apt to occur in individuals with a history of sensitivity to multiple allergens.

There have been well documented reports of individuals with a history of penicillin hypersensitivity reactions who have experienced severe hypersensitivity reactions when treated with a cephalosporin. Before therapy with a penicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, and other allergens. If an allergic reaction occurs, the drug should be discontinued and the patient treated with the usual agents e.g., pressor amines, antihistamines and corticosteroids.

Precautions: Use cautiously in individuals with histories of significant allergies and/or asthma.

Carefully avoid intravenous or intraarterial use, or injection into or near major peripheral nerves or blood vessels, since such injections may produce neurovascular damage.

A small percentage of patients are sensitive to procaine. If there is a history of sensitivity, make the usual test: Inject intradermally 0.1 cc. of a 1 to 2 percent procaine solution. Development of an erythema, wheal, flare or eruption indicates procaine sensitivity. Sensitivity should be treated by the usual methods, including barbiturates, and procaine penicillin preparations should not be used. Antihistaminics appear beneficial in treatment of procaine reaction.

The use of antibiotics may result in overgrowth of nonsusceptible organisms. Constant observation of the patient is essential. If new infections due to bacteria or fungi appear during therapy, discontinue penicillin and take appropriate measures.

If allergic reaction occurs, withdraw penicillin unless, in the opinion of the physician, the condition being treated is life threatening and amenable only to penicillin therapy.

When treating gonococcal infections with suspected primary or secondary syphilis, perform proper diagnostic procedures, including darkfield examinations. In all cases in which concomitant syphilis is suspected, perform monthly serological tests for at least four months.

Adverse Reactions: (Penicillin has significant index of sensitization) skin rashes, ranging from maculopapular eruptions to exfoliative dermatitis; urticaria; serum sickness-like reactions, including chills, fever, edema, arthralgia and prostration. Severe and often fatal anaphylaxis has been reported. (See "Warnings.")

As with other antisyphilitics, Jarisch-Herxheimer reaction has been reported.

Administration and Dosage: Administer only by *deep intramuscular injection,* in upper outer quadrant of buttock. In infants and small children, midlateral aspect of thigh may be preferable. When doses are repeated, vary injection site. Before injection, aspirate to be sure needle bevel is not in blood vessel. If blood appears, remove needle and inject in another site.

Although some isolates of *Neisseria gonorrhoeae* have decreased susceptibility to penicillin, this resistance is relative, not absolute, and penicillin in large doses remains the drug of choice. Physicians are cautioned not to use less than recommended doses.

Gonorrheal infections (uncomplicated)—Men or Women: 4.8 million units intramuscularly divided into at least two doses and injected at different sites at one visit, together with 1 gram of oral probenecid, preferably given at least 30 minutes prior to injection.

NOTE: Treatment of severe complications of gonorrhea should be individualized using large amounts of short-acting penicillin. Gonorrheal endocarditis should be treated intensively with aqueous penicillin G. Prophylactic or epidemiologic treatment for gonorrhea (male and female) is accomplished with same treatment schedules as for uncomplicated gonorrhea.

Retreatment: The National Center for Disease Control, Venereal Disease Branch, U.S. Dept. H.E.W. recommends:

Test cure procedures at approximately 7-14 days after therapy. In the male, a gram-stained smear is adequate if positive; otherwise, a culture specimen should be obtained from the anterior urethra. In the female, culture specimens should be obtained from both the endocervical and anal canal sites.

Retreatment in males is indicated if urethral discharge persists 3 or more days following initial therapy and smear or culture remains positive. Follow-up treatment consists of 4.8 million units I.M. divided in 2 injection sites at single visit.

In uncomplicated gonorrhea in the female, retreatment is indicated if follow-up cervical or rectal cultures remain positive for *N. gonorrhoeae.* Follow-up treatment consists of 4.8 million units daily on 2 successive days.

Syphilis: all gonorrhea patients should have a serologic test for syphilis at the time of diagnosis. Patients with gonorrhea who also have syphilis should be given additional treatment appropriate to the stage of syphilis.

Composition: Each disposable syringe 2,400,000 units (4-cc. size) contains procaine penicillin G in a stabilized aqueous suspension with sodium citrate buffer, and as w/v approximately 0.5% lecithin, 0.5% carboxymethylcellulose, 0.5% povidone, 0.1% methylparaben, and 0.01% propylparaben. The multiple-dose 10-cc. vial contains per cc. 300,000 units procaine penicillin G in a stabilized aqueous suspension with sodium citrate buffer and approximately 7 mg. lecithin, 2 mg. carboxymethylcellulose, 3 mg. povidone, 0.5 mg. sorbitan monopalmitate, 0.5 mg. polyoxyethylene sorbitan monopalmitate, 1.2 mg. methylparaben, and 0.14 mg. propylparaben.

Five are graduating with honors. How many with VD?

On the average, you can figure the incidence of VD among teenagers at about 900 per 100,000 population.* And growing.

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Syphilis is preferably treated with benzathine penicillin G, which is also the drug of choice for prophylaxis after exposure. Administration of 2.4 million units (1.2 million in each buttock) usually cures most cases of primary, secondary and latent syphilis with negative spinal fluid.

Indications: In treatment of infections due to penicillin G-sensitive microorganisms that are susceptible to the low and very prolonged serum levels common to this particular dosage form. Therapy should be guided by bacteriological studies (including sensitivity tests) and by clinical response.

The following infections will usually respond to adequate dosage of intramuscular benzathine penicillin G.—Venereal infections: Syphilis, yaws, bejel and pinta.

For deep intramuscular injection only.

Contraindications: Previous hypersensitivity reaction to any penicillin.

Warnings: Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported. Anaphylaxis is more frequent following parenteral therapy but has occurred with oral penicillins. These reactions are more apt to occur in individuals with history of sensitivity to multiple allergens.

Severe hypersensitivity reactions with cephalosporins have been well documented in patients with history of penicillin hypersensitivity. Before penicillin therapy, carefully inquire into previous hypersensitivity to penicillins, cephalosporins and other allergens. If allergic reaction occurs, discontinue drug and treat with usual agents, e.g., pressor amines, antihistamines and corticosteroids.

Precautions: Use cautiously in individuals with histories of significant allergies and/or asthma.

Carefully avoid intravenous or intraarterial use, or injection into or near major peripheral nerves or blood vessels, since such injection may produce neurovascular damage.

In streptococcal infections, therapy must be sufficient to eliminate the organism; otherwise the sequelae of streptococcal disease may occur. Take cultures following completion of treatment to determine whether streptococci have been eradicated.

Prolonged use of antibiotics may promote overgrowth of nonsusceptible organisms including fungi. Take appropriate measures should superinfection occur.

Adverse Reactions: Hypersensitivity reactions reported are skin eruptions (maculopapular to exfoliative dermatitis), urticaria and other serum sickness reactions, laryngeal edema and anaphylaxis. Fever and eosinophilia may frequently be only reaction observed. Hemolytic anemia, leucopenia, thrombocytopenia, neuropathy and nephropathy are infrequent and usually associated with high doses of parenteral penicillin.

As with other antisyphilitics, Jarisch-Herxheimer reaction has been reported.

Administration and Dosage: Venereal infections—

Syphilis—Primary, secondary and latent—2.4 million units (1 dose).

Late (tertiary and neurosyphilis)—2.4 million units at 7 day intervals for three doses.

Congenital—under 2 years of age, 50,000 units/Kg. body weight; ages 2-12 years, adjust dosage based on adult dosage schedule.

(Shake multiple-dose vial vigorously before withdrawing the desired dose.) Administer by **deep intramuscular injection** in the upper outer quadrant of the buttock. In infants and small children, the midlateral aspect of the thigh may be preferable. When doses are repeated, vary the injection site. Before injecting the dose, aspirate to be sure needle bevel is not in a blood vessel. If blood appears, remove the needle and inject in another site.

Composition: Units benzathine penicillin G (as active ingredient): 2,400,000 units in 4-cc. single dose disposable syringe. Each disposable syringe also contains in aqueous suspension with sodium citrate buffer, as w/v approximately 0.5% lecithin, 0.6% carboxymethylcellulose, 0.6% povidone, 0.1% methylparaben, and 0.01% propylparaben. 300,000 units per cc.—10-cc. multi-dose vial. Each cc. also contains sodium citrate buffer, approximately 6 mg. lecithin, 3 mg. povidone, 1 mg. carboxymethylcellulose, 0.5 mg. sorbitan monopalmitate, 0.5 mg. polyoxyethylene sorbitan monopalmitate, 1.2 mg. methylparaben, and 0.14 mg. propylparaben.

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Gallium-67 for the Diagnosis and Localization of Subphrenic Abscesses

G. BRUCE HOPKINS, MD, *and* CHRISTIAN W. MENDE, MD, *La Jolla, California*

Four septic patients with suspected subphrenic abscess were evaluated with gallium-67 citrate and technetium-99m labeled radiopharmaceuticals. Gallium-67 scintigraphs proved instrumental in correctly diagnosing and localizing one left and three right subphrenic abscesses. Gallium-67 scintigraphy can be a useful noninvasive technique for evaluating patients with suspected subphrenic abscess.

SUBPHRENIC ABSCESSES continue to present a challenging clinical problem. They generally occur spontaneously, most frequently as complications of injuries, diseases or operations of the gastrointestinal tract and less frequently as the result of similar lesions of the genitourinary tract.[1] Because of their insidious onset and obscure nature, diagnosis and localization are difficult and often delayed.[2] This is well attested to by mortality figures that range from 32 percent to 56 percent or higher if multiple abscesses coexist.[3,4] Routine noninvasive techniques used to evaluate these patients, including chest and abdominal roentgenograms, abdominal ultrasonography and combined liver-lung scintigraphy, frequently yield equivocal or misleading results due to complicating clinical features such as basilar atelectasis, pleural or peritoneal effusions, pulmonary emboli, chronic obstructive pulmonary disease or cysts.

The principle interest in gallium-67 (^{67}Ga) has centered on its tumor-localizing properties.[5-7] Although investigators have noted ^{67}Ga localization in inflammatory lesions[8] and in experimentally produced abscesses,[9] its use in septic patients has received little emphasis. Littenberg and coworkers[10] recently reported focal ^{67}Ga accumulation in 11 septic patients. In all 11 the region delineated by scintigraphy proved to be the source of sepsis. Gallium-67 localization in hepatic abscesses and acutely inflamed gallbladders has also been recorded.[11,12] This report is addressed to the use of ^{67}Ga in patients with suspected subphrenic abscess.

Methods and Materials

Gallium-67 (^{67}Ga) is a cyclotron-produced radionuclide supplied as a sterile and pyogen-free citrate by several commercial manufacturers. It decays by electron capture, has a physical half-life of 78 hours, and produces gamma rays with energies of 93, 184, 296 and 388 kilo electron volts (kev), which are suitable for imaging with either scintillation cameras or rectilinear scanners.

Technetium-99m (^{99m}Tc) decays with a six-hour physical half-life emitting monoenergetic 140

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kev gamma radiation. The liver and spleen were visualized using ^{99m}Tc-sulfur colloid while ^{99m}Tc-human albumin microspheres were used to image the lungs. These agents were prepared in the Nuclear Medicine Laboratory from commercially available kits.*

Three studies commenced six hours and the fourth ten hours following the intravenous administration of 3 to 5 millicuries (mc) of ^{67}Ga citrate. The studies were made on a Searle Pho-Gamma III-HP scintillation camera using the 184 or 296 kev photopeaks, a 20 percent window and a medium energy diverging collimator. Combined liver-lung, liver-spleen, or lung scintigraphs using 2 mc of ^{99m}Tc-sulfur colloid and 2 mc of ^{99m}Tc-human albumin microspheres were obtained at the same time. When doing the combined liver-lung study, the liver was imaged before injection of the ^{99m}Tc-human albumin microspheres for lung imaging. The 140 kev photopeak of ^{99m}Tc differs sufficiently from the 296 kev photopeak of ^{67}Ga so that combined studies using both radiopharmaceuticals are possible. The patient is maintained in the same position and single or double exposures, using window settings for ^{67}Ga and ^{99m}Tc respectively, are made on polaroid film. This can provide additional helpful information as illustrated in the case reports.

Results

Four septic patients with suspected subphrenic abscess were evaluated with ^{67}Ga citrate and ^{99m}Tc labeled radiopharmaceuticals. Gallium-67 scintigraphs proved instrumental in correctly diagnosing and localizing one left and three right subphrenic abscesses. Each case was confirmed by surgical procedure or drain placement. One patient (Case 2) had amoebiasis with secondary infection by enteric bacteria. The abscesses in the remaining patients contained a mixture of enteric organisms. Two patients with right subphrenic abscess had equivocal results using ^{99m}Tc labeled radiopharmaceuticals and the conventional liver-lung imaging technique. Gallium-67 scintigraphs in both patients clearly gave abnormal findings (Cases 3 and 4).

*New England Nuclear Technetium-99m Sulfur Colloid Kit; 3M Brand Human Albumin Microsphere Kit.

Figure 1.—(Case 1) Roentgenogram of the chest showing atelectasis and consolidation of the left lower lobe.

Reports of Cases

CASE 1. A 45-year-old man was admitted to Scripps Memorial Hospital with fever, temperatures spiking to 102.8°F (39.3°C), chills and left costovertebral tenderness. The patient had been discharged five weeks earlier following a left pyelonephrolithotomy and insertion of a left nephrostomy tube. On admission a chest roentgenogram showed atelectasis and consolidation of the left lower lobe (Figure 1). Findings on an ultrasound study were consistent with a left subphrenic mass. Gallium-67 scintigraphy showed a large focus of ^{67}Ga localization in the left subphrenic area. A combined study using ^{99m}Tc labeled human albumin microspheres to image the lungs proved helpful in placing the ^{67}Ga

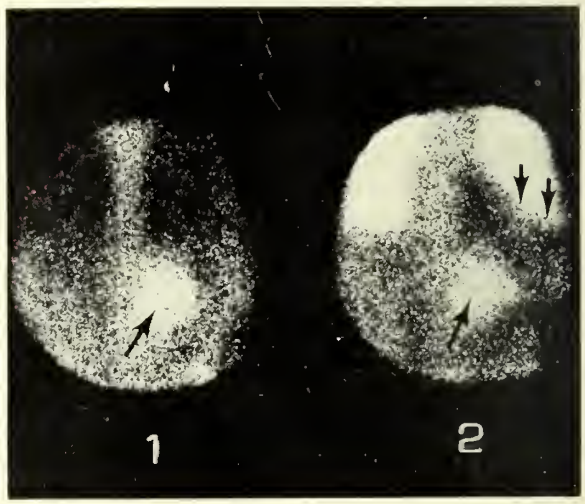

Figure 2.—(Case 1) Anterior chest. **Left,** ^{67}Ga citrate scintigraph (1) shows ^{67}Ga localization at the base of the left lung. **Right,** a combined ^{67}Ga citrate-^{99m}Tc-human albumin microsphere study (2) shows the ^{67}Ga localization to be below rather than within the left lower lobe (see Figure 1).

localization below rather than within the consolidated left lower lobe (Figure 2). A left subphrenic abscess containing Escherichia coli and enterococci organisms was found at surgical operation.

CASE 2. A 44-year-old man was admitted to the hospital with fever, jaundice, weight loss, abnormal findings on liver function tests and a right chest empyema. Roentgenograms showed opacification of the right lung. Liver scintiphotos using ^{99m}Tc labeled sulfur colloid showed a focal defect in the dome of the right hepatic lobe. Gallium-67 scintigraphy showed pronounced ^{67}Ga localization at the same site with extension into the subphrenic space and the right side of the chest (Figure 3). On exploratory operation, a perforated diaphragm secondary to an abscess involving the dome of the liver and right subphrenic space was noted, with extension into the right pleural space and right lung. Purulent material from the abscess cavity contained amoebic cysts and bacteroides organisms.

Figure 3.—(Case 2) Anterior liver: **Left,** the ^{99m}Tc sulfur colloid scintigraph (1) shows a defect in the dome of the right hepatic lobe. **Right,** a ^{67}Ga citrate scintigraph (2) obtained in the same position shows ^{67}Ga localization at the same site with extension into the right subphrenic space and right chest.

CASE 3. A 24-year-old woman was admitted with granulomatous colitis and multiple colon perforations. One month after colectomy, fever developed with temperatures spiking to 103°F (39.4°C). A roentgenogram of the chest showed elevation of the right hemidiaphragm. Combined liver-lung scintigraphs using ^{99m}Tc labeled radiopharmaceuticals were equivocal for evidence of a right subphrenic abscess. Gallium-67 scintigraphs clearly showed abnormal ^{67}Ga localization in the right subphrenic space (Figure 4). Drainage of the abscess yielded a mixture of E coli and enterococci organisms.

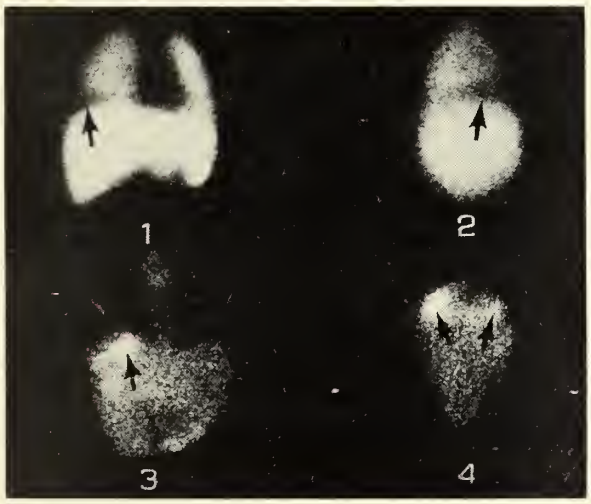

Figure 4.—(Case 3) Anterior (1) and right lateral (2) liver-lung scintigraphs using ^{99m}Tc-sulfur colloid and ^{99m}Tc-human albumin microspheres are equivocal for evidence of a subphrenic abscess while similar views in the same positions (3,4) using ^{67}Ga citrate clearly show ^{67}Ga localization in the right subphrenic space. Note that the loculated posterior abscess seen with ^{67}Ga citrate (4) is not evident on the ^{99m}Tc study (2).

CASE 4. A 53-year-old man became febrile and lethargic one week following operation for a ruptured appendix and periappendiceal abscess. A roentgenogram of the chest showed elevation of

Figure 5.—(Case 4) **Left,** right lateral liver-lung scintigraph (1) using ^{99m}Tc-sulfur colloid and ^{99m}Tc-human albumin microspheres shows posterior separation of the hepatic and pulmonary images. **Right,** a ^{67}Ga scintigraph (2) obtained in the same position shows ^{67}Ga localization in the area of separation.

the right hemidiaphragm. Results of combined liver-lung scintigraphs using ^{99m}Tc labeled radiopharmaceuticals were equivocal with separation of the hepatic and pulmonary images present on only the right lateral view. A ^{67}Ga scintigraph showed ^{67}Ga localization in the area of separation (Figure 5). E coli, enterococci and bacteroides organisms were cultured from the abscess cavity.

Discussion

The scintigraphic finding associated with right subphrenic abscess using ^{99m}Tc labeled radiopharmaceuticals and combined liver-lung imaging technique is separation of the hepatic and pulmonary images on anterior and right lateral or posterior and right lateral views. Displacement of the liver may occur with large abscesses. The result is a cold spot or negative defect lacking specificity. Emphysema, pulmonary emboli, cirrhosis, cysts or pleural and peritoneal effusions may all yield similar scintigraphic findings.[4] The use of ^{67}Ga citrate can increase the specificity of diagnosis by eliminating these noninflammatory causes of false positive liver-lung studies. The number of false negative or equivocal studies may also be reduced as illustrated by two of our cases. Gallium-67 scintigraphy should prove even more valuable in left subphrenic abscess as conventional liver-lung imaging in this area is difficult and unreliable due to the position of the heart and variability in size and position of the left hepatic lobe and spleen.[4]

The current technique observed in most laboratories for ^{67}Ga tumor surveys is to delay scintigraphy 48 to 72 hours following intravenous injection, to insure maximal target-to-background ratios. This delay is unnecessary in septic patients due to the avidity of ^{67}Ga for inflammatory sites. Abscess-to-background ratios sufficient for interpretable scintigraphs may be obtained as early as two hours postinjection.[10]

Clinical and experimental studies suggest that the localization of ^{67}Ga in inflammatory sites is mediated by binding of the radionuclide to intact granulocytes.[13,14] Gallium-67 has been shown to concentrate in granulocytic organelles resembling lysosomes.[15] The increased lysosomal activity of granulocytes may explain the rapid accumulation and subsequent early detection of ^{67}Ga in inflammatory sites. A decrease in circulating granulocytes has correlated with both a diminution in intensity and a delay in onset of ^{67}Ga detection in experimental inflammation.[13]

One potential source of error would be diagnosing subphrenic abscess in a patient with primary or metastatic liver cancer. Generally, the clinical setting of the patient with sepsis is sufficiently different from patients with cancer so that this should not prove a significant problem. If tumor is suspect, positive results should be considered nonspecific and other diagnostic modalities employed.

Whether ^{67}Ga scintigraphy will prove superior to other noninvasive techniques remains to be answered. Based on our limited experience, it does appear to be a valuable adjuvant in the diagnosis and localization of subphrenic abscesses.

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Arthrocentesis of the Knee in Acute Hemophilic Arthropathy

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In 27 children and young adults with hemophilia presenting acutely painful distended intra-articular hemorrhages of the knee, aspiration was carried out and the patients were followed for a minimum of 24 months. Seventeen patients with classical hemophilia were found to have less than 1 percent of normal plasmal level of antihemophilic factor (AHF). Of the remainder, five were Factor IX, plasma thromboplastin component (PTG), deficient, whereas two patients had Von Willebrand's disease. Aspiration was routinely done in an outpatient clinic, followed by immediate discharge with return to regular activity levels within 48 hours. There were no infections nor rehemorrhages attributable to aspiration technique.

MANAGEMENT OF CHRONIC DISABILITY caused by joint hemorrhage in patients with hemophilia has been a concern for many years. Recurrent blood loss, especially into the knee joint where incidence is highest,[1-5] creates a vicious cycle of inactivity and progressive disability.

Many clinicians treating patients with hemophilia mention aspiration of the acutely distended joint[2,3,6,7] as a desirable adjunct to therapy but little mention is made of technique, hematologic control or long-term effectiveness. Petersen[8] reported one instance of death from streptococcal infection following knee joint aspiration and it is presumed that many physicians have abandoned aspiration for similar though less catastrophic reasons.

Trueta[9] described the vicious cycle of joint destruction. Intra-articular blood under pressure produced painful joint distention and muscle imbalance about the knee with compression of the opposing hyaline cartilage surfaces. Further damage to the articular cartilage was caused by subchondral and synovial ischemia due to decreased blood flow. De Palma[2] classified four stages of a progressively destructive process; irreversible changes were found by Stage Three.

Although the often quoted figure of 20,000 to 40,000 persons with hemophilia in the United States is unsubstantiated, the general incidence is estimated at one per ten thousand males.[10] Of this group, 80 percent have Factor VIII—antihemophilic factor (AHF)—deficiency (hemophilia A, classical hemophilia) and 15 percent have Factor IX—plasma thromboplastin component (PTC)—deficiency (Christmas disease, hemophilia B). In both types, there is recurrent hemarthrosis. Lacking a documented study of aspiration of the acutely distended joint and facing a large hemophilic population, this feasibility study was under-

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taken to attempt to decrease the morbidity and the long convalescent period inherent in this joint disorder.

Material

Subjects were selected from the population of 400 patients with hemophilia cared for at the Regional Hemophiliac Rehabilitation Center at the Orthopaedic Hospital in Los Angeles. Patients were candidates for this study when they were seen for administration of plasma products for acute hemarthroses of the knee and when distention, limitation of motion and acute pain or discomfort were noted in the joint. The suprapatellar pouch was uniformly distended in the less chronically affected joints. Distention was less evident in those joints with advanced degenerative changes of soft tissue scarring and contracture; however, pain appeared more severe in the more severely degenerated joints. Plasma levels of Factor VIII as determined by the two-stage technique were known and the severity of the disease was classified according to Nilsson's rating.[11] (See Table 1.)

Variables studied were duration of hemorrhage, x-ray rating of the aspirated joint, knee circumference, range of motion, volume, cell count and hematocrit of the aspirated material and the walking-activity level. Measurements were taken of the circumference of the knee at both the midpatella and one and two inches above and below this site, plus joint ranges of motion immediately before and at regular intervals after aspiration.

TABLE 1.—*Description of Subjects*

1. *Type of Hemophilia*

	Patients
Antihemophilic factor (AHF) deficient	20
Plasma thromboplastin component (PTC) deficient	5
Von Willebrand's disease	2
TOTAL	27

2. *Severity of Hemophilia*

Plasma levels of AHF or PTC factors (2 stage technique)	*Hemo A (AHF Deficient)*	*Hemo B (PTC Deficient)*	*Von Will.*
5 to 25% of normal (mild)	1	0	0
1 to 5% of normal (moderate)	2	0	0
Less than 1% of normal (severe)	17	5	2
Untested	0	0	0
TOTALS	20	5	2

3. *Age*

Mean	13.4 years
Median	11.5 years
Range	6-35 years

4. *Duration of Hemorrhage*

Mean	2.2 days
Median	1 day
Range	3 hours to 14 days

5. *Cause*

Spontaneous	25
Traumatic	2

Following baseline measurements, an infusion of intravenous glucose and water was started. Under sterile conditions with 1 percent lidocaine hydrochloride (Xylocaine® hydrochloride) anesthesia, arthrocentesis was carried out with a 15 gauge needle from the most accessible site adjacent either to the medial or lateral superior poles of the patella. Following aspiration, 1 ml each of dexamethasone sodium phosphate (Decadron®) and prednisolone tertiary-butylacetate (Hydeltra®-TBA) diluted to 6 ml with 1 percent hydrochloride were instilled into the joint in an effort to reduce the local inflammatory response.[12] Plasma products were then administered, with AHF deficient patients receiving sufficient concentrate or cryoprecipitate to raise their AHF levels to 50 percent. PTC deficient patients received the maximum amount of lyophilized plasma, calculated by body weight, that could be administered without overloading the cardiovascular system. This raised their PTC levels to between 15 and 20 percent. A sterile compress and an elastic wrap were applied to the knee, followed by a posterior molded thermoplastic splint for 24 hours.

Patients were then seen following aspiration (defined as day 0) on days 4, 7, 14 and 28, and at six and eight weeks. Plasma products were administered to attain factor levels of 20 percent on days four and seven, walking with crutches was begun on day one and crutches were discontinued by day four. The molded thermoplastic splint with an open anterior thigh was used for 24 hours and supervised exercises under a therapist's direction were begun day four.

Results

During the first year of this investigation, aspirations were carried out on 27 patients, equally on the right and left knees. Characteristics of the joint aspirate are listed in Table 2.

A mild elevation in cell count would indicate that hemophilic arthropathy should be included in the Grade 1 classification of Ropes and Bauer,[13] along with traumatic effusions and osteoarthritis.

Current anteroposterior and lateral x-ray views

were evaluated for the severity of degenerative changes. De Palma's[2] classification ranging from earliest detectable changes (Grade 1) to far advanced fixed deformities (Grade 4) were used. The median grade of degenerative changes in 27 patients was 2 with a range of 0 to 4.

Loss in knee extension varied between 5 degrees and 60 degrees at the time of aspiration with improvement to between 0 and 45 degrees by day four. Total range of motion ranged from 0 to 110 degrees at the time of aspiration and improved to between 40 and 140 degrees on day four. A mean gain of 21 degrees of knee extension was noted and a mean overall increase of range of motion of 65 degrees was evident. By eight weeks the total range of motion averaged 97 degrees and loss of knee extension measured only 8 degrees. Circumference measurements decreased by an average of 2.2 cm by the fourth day after aspiration, with little change thereafter (see Table 3).

Within the eight week period arbitrarily designated as recovery from an acute hemarthrosis, there was spontaneous recurrence of blood loss in nine knees; in two knees during the fourth week, five during the sixth week and two during the eighth week. The mean age of the rehemorrhage group was 12.7 years, with a mean x-ray rating grade of 2. One patient was lost to follow-up due to hepatitis developing in the second week after aspiration.

Most significant was the return of all aspiration candidates to normal school and employment activities within 48 hours of aspiration. In no instance could rehemorrhage be attributed to the operation technique. There were no instances of infection.

Attempting numerous correlations of the first year's findings showed an inverse relationship between x-ray rating and volume of aspirate. As noted earlier a knee joint with advanced degenerative changes has a reduced joint volume. Similarly, a decreased cell count was noted with increasing aspirate volume; this may represent a dilutional effect.

During the second year of this study 24 of the original 27 patients were followed for a total of 24 months. Ten remained free of blood loss in joints, whereas 14 required repeat aspiration. At the end of 24 months, 12 patients were walking without artificial support, whereas, 12 required the assistance of a posterior splint or crutches, or a brace.

A review of hospital records was made to ascertain the frequency of blood losses into the affected joints for the immediate two years before beginning aspiration treatment. The chi-square of analysis was of only marginal significance in analyzing the frequency of blood losses in the aspiration versus preaspiration groups.

TABLE 2.—*Aspirate Analysis*

1. *Volume (N=27)*	
Mean	73.2 ml
Median	70.0 ml
Range	15 to 200 ml
2. *Cell count (N=23)*	
Mean	3,460 cells per cu mm
Median	2,750 cells per cu mm
Range	600-9,000 cells per cu mm
3. *Hematocrit (N=26)*	
Mean	31.9%
Median	33.5%
Range	6.0%

TABLE 3.—*Range of Knee Motion*

	Aspiration Day (degrees)	*Day 4 (degrees)*	*Weeks 6 to 8* (degrees)*
Loss of terminal knee extension (mean)	35.4	14.6*	8.7
Total motion (mean)	28.9	94.4	106

*26 patients only.

TABLE 4.—*Comparative Knee Circumference Measurements*

	Aspiration Day (centimeters)	*Day 4 (centimeters)*	*Weeks 6 to 8* (centimeters)*
Maximum circumference (mean)	32.6	30.4	30.1

*N=26 subjects.

Discussion

Aspiration of the acutely distended, painful, joint in hemophilic arthropathy is a safe and effective procedure when undertaken with rigid aseptic technique and adequate replacement therapy. Before instituting aspiration techniques in a patient with a serious intra-articular bleeding episode, an average of three to seven days in the hospital would be required with cast or traction immobilization followed by an often prolonged convalescence. The 27 patients making up this series represent a consecutive prospective series selected only by virtue of the relative severity of their intra-articular hemorrhages. All were treated as outpatients and discharged to their homes within three hours. All patients followed for the 24

months duration of the study were able to resume their usual and customary activity level within 48 hours of aspiration. There was no instance of infection or rchemorrhage attributable to this procedurc. Strict aseptic technique, replacemcnt therapy to the 50 percent concentration level and appropriate temporary splintage were essential to this rapid rehabilitation.

The exact nature of the toxic agent in recurrent hemarthrosis is unknown. Hemosiderin deposition throughout the synovium and in macrophages beneath the synovial layer, with fibrosis and scarring of the synovium and capsule, precedes articular destruction.[14-17] Recent investigations[18] of the role of lysosome in articular cartilage degeneration have confirmed the original studies of Fell and Dingle,[19] who first delineated the lysosomal acid protease in which the lysosome was shown to be capable of breaking down the polysaccharide of cartilage matrix in vitro. Roy[20] recently described the earliest degenerative changes in the cartilage matrix by using electron microscopy. Many iron-containing bodies, called sideromes, were seen in the chondrocytes of the superficial and middle zones of the articular cartilage of hemarthritic joints. These bodies were seen before any cartilage changes were visible by light microscopy techniques. Roy postulated that lysosomal liberation from these sideromes may initiate the process of cartilage destruction by causing chondrocyte damage.

The mean cell count of 3,460 cells per cu ml, calculated on a sample of 23 aspirants, is only slightly above the normal range for nonspecific traumatic arthritis. This low concentration would suggcst a rather small reservoir for lysosomal enzyme liberation.

It would appear from review of current literature that prevention of the initial intra-articular deposition of hemoglobin is a key factor in preventing the often insidious progression of hemophilic arthritis. Results of preliminary review of prospective prophylactic studies now under way at Orthopaedic Hospital would appear most promising. However, in the treatment of established severe hemarthrosis, the role of aspiration should be considered a safe and effective means of restoring early joint function. The incidence of intra-articular hemorrhage in its relationship to seasonal variations, trauma, type of hemophilia, severity and activity is difficult to document. Although it was the clinical impression that aspiration of the knee decreased the number of recurrent hemarthroses, statistical analysis on this admittedly small number of patients did not verify our clinical impression.

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Suicide Survivors

A Follow-up Study of Persons Who Survived Jumping from the Golden Gate and San Francisco-Oakland Bay Bridges

DAVID H. ROSEN, MD, *San Francisco*

Interviews with seven of ten known survivors of jumps from the Golden Gate and San Francisco-Oakland Bay bridges showed a unique association between the Golden Gate Bridge and suicide. The study went beyond exploring the nature of suicidal jumps and shed new light on the experience of nearly dying. All the survivors described this experience as tranquil and peaceful. None of them experienced life events or distant memories passing through their minds or before their eyes. However, all of them experienced transcendence and spiritual rebirth phenomena. Suggestions for preventing suicides from the Golden Gate Bridge are discussed, including the construction of a suicide barrier.

"After all, it is no more surprising to be born twice than it is to be born once."
—VOLTAIRE

A SUICIDAL LEAP from either the Golden Gate or the San Francisco-Oakland Bay Bridge is almost invariably fatal. Only 1 percent of persons jumping from these bridges survives. This paper is a summary report of a two and a half year follow-up study of these survivors. The research project initially had two objectives: (a) To determine the whereabouts and present condition of the ten known survivors and (b) to interview this rare group to learn more about the nature of suicidal behavior by jumping and its alleged impulsive and ambivalent qualities. I also hoped to answer the following questions: (1) Why the choice of the Golden Gate Bridge? Why is it the number one location for suicides in the world, now with over 535 known suicides since it opened in 1937? (2) Can these persons recall the suicidal jumps and the experiences of nearly dying? (3) Did their life's memories pass through their minds or in front of their eyes? (4) Did they lose consciousness? (5) How have the survivors subsequently handled such an upsetting traumatic event—an experience so close to death? (6) What have been the long-term effects of such events on their lives?

The potential benefits for suicide prevention resulting from a clearer understanding of attempted suicide by jumping and its effect on the individual person seemed to the author to outweigh any possible risk to the subjects involved in this study.

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Submitted January 3, 1975.

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Methods

Although it has proven difficult to locate the ten survivors despite using systematic follow-up techniques,[1] it has been possible to interview six of the eight* Golden Gate Bridge survivors and one of the two San Francisco-Oakland Bay Bridge survivors. The initial contact was made by telephone whenever possible. If the subject was under the care of a psychiatrist, permission was sought and obtained from the psychiatrist before interviewing the survivor. The interviews were carried out in accordance with established psychiatric ethics, and care was taken not to pursue matters which the person did not wish to discuss. Each person was made aware that he or she could refuse to answer any of the questions during the interview, and assured that anonymity would be preserved. The goals of the project were explained to each survivor and it was emphasized that their participation was entirely voluntary.

The Golden Gate Bridge Survivors

Demographic characteristics (at the time of the jump)

The eight Golden Gate Bridge survivors were composed of seven men and one woman. The average age was 24 years old and the age range was from 16 to 36 years. One survivor was married, one was divorced and the rest were single. Three out of the eight survivors were in psychiatric treatment (one was an inpatient out on a pass).

Choice of Bridge

All six of the interviewed Golden Gate survivors' suicide plans involved *only* the Golden Gate Bridge. Four of the six said they would not have used any other method of suicide if the Golden Gate Bridge had not been available (for instance, if there had been a suicide barrier).

One survivor associated the beauty of the bridge with death and jumped from it because "I was attracted to the bridge—an affinity between me, the Golden Gate Bridge and death—there is a kind of form to it, a certain grace and beauty. The Golden Gate Bridge is readily available and it is connected with suicide." Another survivor denied that he even attempted suicide by jumping from the Golden Gate Bridge. He associated jumping from the Golden Gate Bridge with entering the "golden doors" in order to leave his body and the material realm and enter into the new spiritual realm. "It was the Golden Gate Bridge or nothing. I believed it was the way."

Another survivor said jumping from the Golden Gate Bridge was "a romantic thing to do," and that it assured "certain death in a painless way." A different survivor described suicide from the Golden Gate Bridge as "easy" and a "sure thing." Another said the Golden Gate is "the only sure way." The remaining survivor said the extensive press coverage and the "notorious fame" that surround the Golden Gate Bridge suicides, plus its "easy accessibility," made it the "only method" of suicide for him.

Reasons for Jumping

The reasons for the suicide attempts varied and included the following: (1) "Problem relating to people . . . no personal love . . . a loner." (2) "Extremely depressed and felt worthless . . . stuttering was uncontrollable . . . longed for death as a release from my feelings of alienation and hopelessness." (3) "Felt alone and didn't know what to do and I wanted to die." (4) "Rejected by my lover." (5) "Life was not worth living . . . nothing interested me." (6) "Depressed, confused, and failing in school . . . jumping and living—a logical way to keep things silent, to get old things finished and to draw attention to myself and issues."

Two subjects heard voices before their jumps: One of them had taken D-lysergic acid diethylamide (LSD) and the voices directed him to go to the Golden Gate Bridge and jump off; the other was asked by a God-like voice, "Why are you doing this? Why are you giving up?" Two other subjects told of bridge employees rushing toward them and yelling at them. Both of these survivors were angered by the way these men approached them and they said they might not have jumped if these men would have calmly walked up and spoken to them in a gentle manner.

Descriptions of the Fall

The distance at mid-span from rail to water is 250 feet and about 260 feet at low tide and it takes just three to four seconds to travel this distance. The velocity in a free-fall from the Golden Gate Bridge has been calculated to range between 73.6 and 75 miles per hour of impact force in each case.[2]

*These eight include the most recent survivor (February 1975) who was added after this paper was submitted for publication. He has not been interviewed.

Only one survivor described a distinct sense of falling through the air rapidly. The other five lost their time orientation and said the fall felt like a long time, from "hours" to "an eternity." This apparent slowing of time has also been found to be the most frequently reported phenomenon (75 percent) in persons undergoing sudden accidental near-death experiences (falls or near-drownings).[3]

The experience of jumping for all six of the survivors was described as tranquil and peaceful and not frightening or terrifying as one might suspect. This is similar to the account mountain climbers give after they have survived accidental falls from great heights.[3-5] One survivor said, "It was a good feeling—no screaming. It was the most pleasant feeling I've ever had. I saw the horizon and the blue sky and I thought how beautiful it was." Another survivor said that at first he had a peaceful feeling and then he felt like he went into a "dream" . . . "I never felt I was dying." One subject stated that he experienced "a sense of relief" and "peace" on the way down. One subject said he "caught a glimpse of San Francisco . . . thoughts of goodbye—leaving San Francisco is like leaving the world. I felt like a bird flying—total relief. In my mind I was getting away from one realm and going to another. I did not struggle. I gave up. I was looking forward to what was to come. Even now I'm symbolically still looking for the better world—I'm still in that place between the bridge and the water." Another reported that his descent was "like eternity—beautiful—I enjoyed the sensation."

Three of the six survivors said they "knew" before they jumped that they would not die. One of these survivors denied any suicidal intent. He was the one who entered the "Golden Doors" to a higher spiritual realm, and he said he was fulfilling a spiritual need. He said, "My jump has more to do with parapsychology than with psychology." Another subject said, "I did not believe for a moment that I would die. The voices said I would not die—and that nothing would happen . . . the voices even said I would be picked up by a fishing boat." One of the survivors left a "suicide" note stating "Why me, can I understand what's beyond death? Is there something outside the realm of understanding to be understood?" He later said, "I never thought I was going to kill myself and die, I knew I was going to survive it. I figured the only thing that separated the ones that lived and died in jumps from the Golden Gate Bridge was the will to live and I had that very strong inside."

None of the six survivors interviewed recalled experiencing life events or distant memories passing through their minds or before their eyes during their jump. One survivor did experience the phenomenon of seeing the image of his father in an approaching bridge employee. It was his opinion that what he experienced was the feeling that his deceased father was coming for him and trying to communicate with him. Another survivor related that he thought of past events during the day before he jumped. Another subject recalled having some thoughts during his descent of being "innocent," and about how nice his mother was.

All but two of the survivors blacked out just before hitting the water; at least they do not remember hitting the water. One subject who described the first half of his descent as "peaceful, enjoyable and fun," realized that halfway down he was going to hit a concrete piling and he remained conscious to solve this problem. He maneuvered his body so that he only grazed the concrete piling. He then nearly drowned but he feels his prayers to God were answered and he was saved. The other subject who remembered hitting the water said, "When I hit the water I felt a vacuum feeling and a compression like my energy displaced the surface energy of the water. At first everything was black, then gray-brown, then *light*. It opened my mind—like waking up. It was very restful. When I came up above the water, I realized I was alive. I felt reborn. I was treading water and singing—I was happy and it was a joyous occasion. It affirmed my belief—there is a higher spiritual world. I experienced a transcendence—in that moment I was refilled with new hope and purpose of being alive." This person's description of spiritual rebirth and transcendence was experienced in varying degrees by all the survivors.

Death-Rebirth Experiences and Spiritual Transcendence

One subject stated, "It was strange because I thought suicide was the right thing to do. Before I jumped I was an agnostic—no real belief in God. After the jump I became fully Christian, I believed in God and Jesus Christ." This same person also said "Christ became a living reality for me." (He felt Christ and his disciples were around him.) "It is still going on. I'm now in a

period of painful growth—of being reborn." Another survivor went to the Golden Gate Bridge with thoughts of being with God. He wished he could visit with God. He thought if God understood and accepted him he would go to "Paradise." This same person, after surviving the jump, said his "will to live had taken over" and he felt that there was "a benevolent God in heaven who permeates all things in the universe." He said we were all members of "the godhead—that great god humanity."

Another survivor said at the time of his jump, "I thought I would go to heaven and I asked forgiveness regarding my committing suicide." Another person said he had a "strong life drive" and his "whole life was reborn," that he "broke out of old pathways" and he can now "sense other peoples' existence." An additional survivor said that he now "loves God" and that he wants to "do things for others." Another said he was glad he didn't die and that after his jump he felt closer to God and he thanks God that he didn't die. A different survivor said, "I was refilled with a new hope and purpose in being alive. It's beyond most people's comprehension. I appreciate the miracle of life—like watching a bird fly—everything is more meaningful when you come close to losing it. I experienced a feeling of unity with all things and a oneness with all people. After my psychic rebirth I also feel for everyone's pain. Surviving reconfirmed my belief and purpose in my life. Everything was clear and bright—I became aware of my relationship with my creator."

Medical Injuries

Only two of the six interviewed survivors had serious medical injuries (for example, ruptured spleen and multiple fractures) after their jumps. The others sustained minor injuries (for example, bilateral clavicle separations) and one had no injuries at all.

Snyder and Snow[2] studied the necropsy reports for 169 suicides from the Golden Gate Bridge and found that only eight persons (5 percent) "died from drowning and not as a result of impact trauma." They also stated that, "These individuals appeared to have impacted in the foot to head orientation." This is very interesting since all six interviewed survivors jumped feet-first and the two who were conscious on impact reported that they landed feet-first as well.

Subsequent Suicidal Behavior

Only one of the six interviewed survivors has made subsequent suicide attempts, and these were by drug overdose. Two of the six survivors were working, two others were planning to obtain some kind of employment, and the remaining two were receiving disability payments.

Suicide Prevention

All six survivors favored the construction of a suicide barrier on the Golden Gate Bridge. Some of their reasons were as follows: (1) "It would be helpful—it would discourage suicidal persons and it would enable people to think about it and possibly change their minds." (2) "It would make it less accessible. Even if it saved one person's life, it would be worth it." (3) "It would make it harder to commit suicide. It would let people struggle through the experience to the bottom of their soul and then maybe they would want to serve people and God."

Other suggestions regarding suicide prevention in general and specifically concerning the Golden Gate Bridge were as follows: (1) "Newspaper editors should voluntarily stop all press coverage of the Golden Gate Bridge suicides—extensive press coverage put the idea into my mind," and (2) "A new church is needed where there is one wise person who could tell people suicide is not where it's at. God should instruct that it is better to serve. Like in my case, God played a hand in it."

The San Francisco-Oakland Bay Bridge Survivor

The two known survivors of jumps from the San Francisco-Oakland Bay Bridge are both women, ages eighteen and thirty. The survivor whom I interviewed jumped from the Bay Bridge because it was the nearest bridge to her home. She said if she would have not been able to jump from this bridge she would have driven to the Golden Gate Bridge and jumped there. She had been upset and depressed because her children had recently been taken away from her. She wanted to commit suicide because she was depressed, felt worthless and useless and without a sense of direction. She had impulsively left her home, driven to the bridge, stopped her car on the bridge, got out and jumped off with the conscious goal of dying. She had been seeing and hearing

her deceased father and she wanted to join him.

When she jumped she thought, "This is the end." She thought she would die and she did not struggle against it. She felt "a tremendous sense of peace." Past life events and memories did not pass through her mind or before her eyes. She remembers hitting the water, "It felt real good—I like to dive. I knew I was alive. At first I felt angry and disappointed I hadn't died. I remember going far down under water and wondering when I would come up. I came up and I didn't feel hurt. After I was picked up by the Coast Guard, I blacked out." She had a serious medical injury (fractured pelvis) which necessitated her remaining in bed for several months.

She did not experience a union with her father as she had hoped. However, she did report experiencing a spiritual rebirth and transcendence: "I felt chosen because I didn't die, I said this in front of the congregation. I was thankful. I cried in front of them. I wanted to help others. I pointed out how sovereign and powerful God is and how little we are and that it's not up to us. I was pure and cleaner inside. I thought somehow I was helping others in the spiritual realm. Others were helped by my testimony—I thought I could save others. I spoke in tongues twice and asked for the church to be united and for everyone to love each other more."

This woman had another spell of depression six months after her suicide attempt and she was admitted to a state hospital. She responded well to the treatment and she has not had a relapse since that time. Also, her children were eventually returned to her. She strongly recommended the construction of suicide barriers on both the San Francisco-Oakland Bay Bridge and the Golden Gate Bridge so that these two bridges would be not accessible for suicidal jumps.

Comment

Noyes[5,6] has outlined three phases which people commonly undergo while going through the experience of nearly dying: (1) *resistance* (recognition of danger, fear, struggle and acceptance of death), (2) *life review* (rapid review of clear images and scenes from the person's entire past) and (3) *transcendence* (state of mystical consciousness or state of ecstasy and spiritual rebirth phenomena). The accounts of the seven survivors differ from the reports of people who have nearly died from sudden accidental causes. The suicide survivors did not experience the phases of resistance and life review. It may be that the volitional aspects of suicide account for the differences. The person who has planned his own death has most likely worked through a lot of the resistance and this may have something to do with why there is no reported struggle against oncoming death. The planned aspect of suicide may also be related to the fact that these survivors did not experience a life review phase. In sudden accidental encounters with near death, a person would probably try to orient himself by matching the acute current traumatic event with past events, and there would be an automatic check or review of his filed memories of past life events. In contrast, for the suicide survivor the event that brings him close to death was planned and rapid orientation and matching to prior experience would not be required.[7]

However, the "suicide" survivors did consistently experience the transcendence phase of near death. This may have occurred because the majority of the survivors fully expected to die yet they lived. Most reported a feeling of submission or surrender, as if they were guided or controlled by God or a higher power. The survivors reported emotions of extreme calm and peace or ecstasy. They have gone through a unique experience of surviving planned and almost certain death. All the subjects reported in varying degrees spiritual rebirth experiences which are similar to previous reports of religious and transpersonal experiences.[8-12] Most of the survivors, during and after their jumps, experienced mystical states of consciousness characterized by loss of the conventional senses of time, space and self. And they experienced a sense of oneness or unity with other human beings and the entire universe.

The suicide survivors' death-rebirth experience represents both an ego-death (a feeling of total annihilation) and a rebirth (with feelings of love and salvation).[9] I believe it is this experience of ego-death and subsequent spiritual rebirth that is behind the survivors' unified and firm position on the need to construct a suicide barrier on the Golden Gate Bridge. This is probably a projection of a change that has taken place within the survivors, for none of them have gone on to commit suicide. Grof has reported[10] the disappearance of severe suicidal tendencies after patients have experienced final ego-death. This study corroborates Grof's statement, "After the ego-death the individual sees human existence in a much broader

spiritual framework—no matter what the personal problems are, suicide does not appear to be a solution anymore."[10]

It has been reported[13] that the ingestion of hallucinogens lessens the fear of death. This is pertinent, since one of the survivors reported taking LSD just before jumping from the Golden Gate Bridge.

The six Golden Gate Bridge survivors' suicide plans involved *only* the Golden Gate Bridge. For all of them, this bridge had a special and unique meaning. Often this was related in a symbolic way to the association of the Golden Gate Bridge with death, grace and beauty. The fact that the Golden Gate Bridge leads the world as a location for suicides should be knowledge enough for us to begin to *deromanticize* suicide, specifically as it relates to the Golden Gate Bridge, but also in a general way.[14] In addition to *deromanticizing* suicide and death especially as they relate to the Golden Gate Bridge, these findings point to a need to do something practical in order to prevent further suicides from that structure. I underscore and concur wholeheartedly with the survivors' unanimous recommendation that a suicide barrier should be constructed on the Golden Gate Bridge.

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Specialty Conference

Moderator
JOHN Z. MONTGOMERIE, MD

Discussants
A. JAMES LEWIS, MD
MILAN FIALA, MD
MATTHEW O. LOCKS, MD
THOMAS T. YOSHIKAWA, MD
JERROLD A. TURNER, MD

This is a transcript of one of the regular teaching conferences in Infectious Diseases held weekly at Harbor General Hospital, Torrance, California. These conferences have been edited by Doctors Jerrold A. Turner, John Z. Montgomerie, Anthony W. Chow, Thomas T. Yoshikawa and Lucien B. Guze.

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Pericarditis

JOHN Z. MONTGOMERIE, MD:* *Pericarditis has many diverse causes. Today we are examining the infectious causes of pericarditis.*

The infectious agents that may cause pericarditis include in order of frequency, viruses, Mycobacterium tuberculosis, other bacteria, fungi and animal parasites. The infections will be discussed in this order after Dr. Lewis reviews the hemodynamics and diagnostic features of pericarditis. Table 1 has been included to remind you of the noninfectious causes of pericarditis.

Hemodynamic and Diagnostic Features of Pericardial Disease

A. JAMES LEWIS, MD†

I WILL DISCUSS BRIEFLY the hemodynamic features and diagnostic aspects of acute pericarditis, pericardial effusion including tamponade and constrictive pericarditis.

Acute Pericarditis

Acute pericarditis per se does not interfere with normal cardiac function. Evidence of heart failure may occur, however, when there is a prominent component of myocarditis or some other myocardial disease such as acute myocardial infarction.

Precordial pain in pericarditis is frequently affected by respiratory movements, cough and position, whereas chest pain is usually steady and crushing in myocardial infarction. The primary feature of acute pericarditis on physical examination is the presence of a pericardial rub. Typically, the rub is triphasic consisting of a presystolic component corresponding to atrial systole, a systolic component, and an early diastolic component. In the presence of tachycardia or delayed atrioventricular conduction the presystolic and early diastolic components may fuse, giving rise to a so-called summation rub. In a recent report of 50 cases of acute pericarditis[1] the classic triphasic rub was present in 58 percent of cases. In 24 percent, a biphasic rub was present. This consisted of either a combination of presystolic and systolic components, systolic and early diastolic components (such as would be seen in the presence of atrial fibrillation), or a systolic component plus a summation diastolic rub. In 18 percent of cases a monophasic rub was present. This usually consisted of a systolic component, but in one case the presystolic component was the only manifestation.

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TABLE 1.—*Noninfectious Causes of Pericarditis*

Rheumatic fever
Hypersensitivity diseases (Serum sickness)
Rheumatoid arthritis
Collagen diseases
Sarcoidosis
Uremia
Neoplasms and leukemia
Local trauma
Cardiac operation
Myocardial infarction
Dressler's Syndrome
Radiation
Drugs

Typical changes of acute pericarditis are also found on electrocardiograms. The electrocardiographic changes initially involve an elevation of the ST segment consistent with subepicardial injury. The ST segment vector is directed both anteriorly and inferiorly. In a recent report by Surawicz and Lasseter,[2] ST segment elevation was most frequently noted in leads I, II, V5 and V6. ST segment elevation is also commonly noted in the mid precordial leads. Reciprocal ST segment depression is typically present in the aVR lead. Commonly, the ST segment in V1 is isoelectric or may be depressed. Widespread T wave inversion indicative of a superficial myocarditis develops in those leads in which ST segment elevation occurred. It is not well appreciated that an abnormality of the PR segment indicative of subepicardial atrial injury is also frequently seen. The PR vector points to the left and superiorly and is typically negative in leads II, aVF and V4 through V6.

The evolution of the electrocardiographic changes in acute pericarditis has been well described by Spodick and has been divided into four stages.[3] In stage 1, pronounced ST segment elevation is present and depression of the PR segment may be noted (Figure 1). In stage 2, the ST segment begins to return toward the isoelectric line, the amplitude of the T wave diminishes and the PR segment is depressed (Figure 2). By stage 3, the ST segment has returned to the isoelectric line and T wave inversion has occurred. In stage 4, the electrocardiographic changes have resolved. A progression through each of these four stages is considered pathognomonic of acute pericarditis.

Atrial arrhythmias such as premature atrial contractions, atrial tachycardia, atrial flutter or atrial fibrillation may also be seen during the course of acute pericarditis.

Pericardial Effusion and Tamponade

The accumulation of intrapericardial fluid results in a rise of intrapericardial pressure. The degree to which intrapericardial pressure rises is a function both of the speed of fluid accumulation and of the compliance of the pericardium. With the slow accumulation of fluid large volumes of

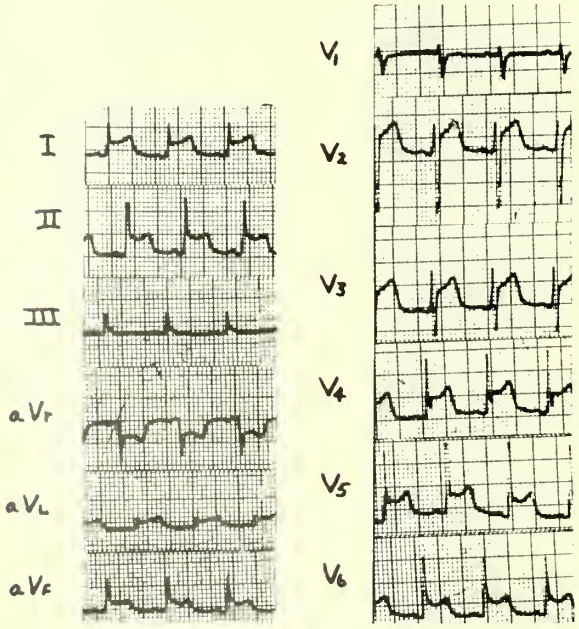

Figure 1.—Electrocardiogram in acute pericarditis stage 1. See text for description.

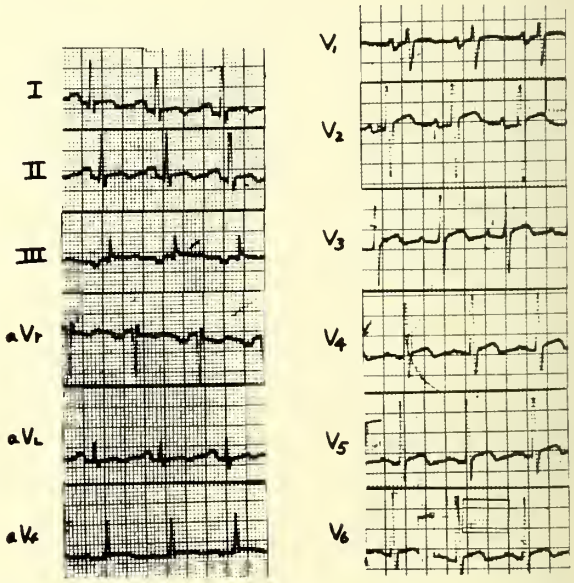

Figure 2.—Electrocardiogram in acute pericarditis stage 2. Note the depressed PR segment (by comparison to the preceding RP segment), well seen in leads I, II and aVL. See text for further description.

intrapericardial fluid can be accommodated because of the gradual expansion of the parietal pericardium. At a certain point, however, the ability of the parietal pericardium to expand further is limited resulting in the abrupt rise in intrapericardial pressure with the further accumulation of small volumes of fluid. This fact has important therapeutic considerations when one is faced with carrying out pericardiocentesis on a patient with pericardial tamponade. The removal of relatively small volumes of intrapericardial fluid may dramatically relieve the hemodynamic deficit present. When pericardial fluid accumulates at a rapid rate, pronounced elevations in intrapericardial pressure may occur with much smaller volumes of fluid.

The major hemodynamic deficit that results from the presence of significant pericardial effusion is the restriction of ventricular filling.[4-6] The mechanism is quite different from that present in constrictive pericarditis. In the presence of effusion there is a fluid medium exerting pressure within the pericardial space as opposed to a rigid restrictive pericardium in the case of constrictive pericarditis. During ventricular systole in the case of pericardial effusion there is a shift of intrapericardial fluid toward the ventricles. This occurs because the intrapericardial volume occupied by the ventricles diminishes with ventricular contraction while that occupied by atria increases displacing fluid toward the ventricles. Hence, in early diastole the ventricles are not able to readily expand resulting in a restriction to the inflow of blood from the atria. Hemodynamically there is an elevation of pressure throughout diastole in the ventricles. In order to maintain some ventricular filling the atrial pressure must also rise and to maintain atrial filling, venous pressure must become elevated. As the restriction to ventricular filling becomes more pronounced there is a drop in ventricular stroke volume. Two compensatory mechanisms are then activated in order to maintain cardiac output: peripheral arteriolar vasoconstriction and tachycardia.

With further increase in intrapericardial pressure there is continued elevation of ventricular diastolic pressure and atrial pressure with a narrowing of the atrioventricular and venoatrial gradients. This results in a further reduction in stroke volume. This may be manifested by a drop in systolic blood pressure. When the compensatory mechanisms are no longer able to maintain cardiac output the stage of cardiac tamponade has been reached. Hemodynamically there is an elevation of ventricular pressure throughout diastole, a lowered end-diastolic ventricular volume and decreased cardiac output. In addition, the atrioventricular and venoatrial gradients necessary for the forward flow of blood through the heart become critically narrowed.

Physical findings in a patient with pericardial tamponade are dependent upon the hemodynamic deficits present. As mentioned, in order to maintain stroke volume the venous pressure must rise. With the onset of ventricular systole there is a release of the intrapericardial pressure against the atrial wall, as well as a descent of the atrioventricular valve ring resulting in an increase in intraatrial volume. There is hence a rapid flow of blood into the atria. This is manifest in the jugular venous pulse as a rapid X descent. Because of the restriction of ventricular filling, including early diastole, the Y descent is not prominent and as the intrapericardial pressure rises the Y descent may be lost entirely and replaced by a positive wave.[7] This is in contrast to the rapid Y descent seen in constrictive pericarditis. Tachycardia is usually present in order to maintain cardiac output. As the stage of tamponade is approached there is a drop in systolic blood pressure with maintenance of diastolic pressure resulting in a drop in pulse pressure.

The presence of pulsus paradoxus indicates significant pericardial effusion. In order to demonstrate this sign the patient must be recumbent and breathing normally. One then elevates the blood pressure cuff pressure until all Korotkoff sounds disappear and then slowly releases the pressure. When pulsus paradoxus is present, the initial systolic sounds will be heard only during expiration and will disappear during inspiration. Pulsus paradoxus is measured between the initial appearance of expiratory systolic sounds and the appearance of sounds during both phases of respiration. This difference is normally no greater than 10 mm of mercury. It was termed paradoxic by Kussmaul because he noted that during inspiration the arterial pulse disappeared.

Several theories have been advanced to explain the phenomenon of pulsus paradoxus. One attractive explanation is that in severe pericardial effusion or tamponade the normally present gradient between pulmonary artery and left atrium tends to equalize or even reverse.[7] This probably results from a proportionately greater increase in capacitance of pulmonary vasculature than of the intrapericardial structures during inspiration.

Kussmaul's sign is also occasionally noted in significant pericardial effusion. This consists of an increase in central venous pressure during inspiration (a reversal of the normal situation) resulting from a restriction of ventricular filling.

On x-ray films of the chest, the cardiac silhouette is enlarged and often assumes a globular appearance. Despite even pronounced cardiac enlargement there is very little evidence of pulmonary venous congestion in the typical patient. A finding in x-ray studies is the rapid appearance of cardiac enlargement especially in the absence of pulmonary venous hypertension. In the presence of pericardial effusion a lateral view of the chest may show a wide separation of the epicardial fat line from the sternum. Normally, this rather thin lucent line is immediately adjacent to the sternum, but with the accumulation of intrapericardial fluid it becomes significantly displaced posteriorly.

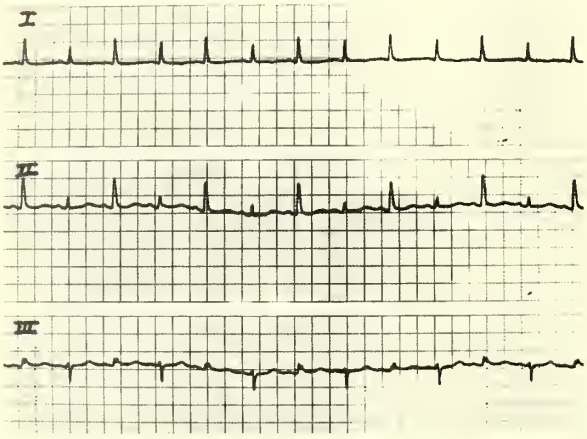

Figure 3.—Electrical alternans. Simultaneously recorded leads I, II and III showing alteration of the QRS complex in every other beat in a patient with pericardial tamponade.

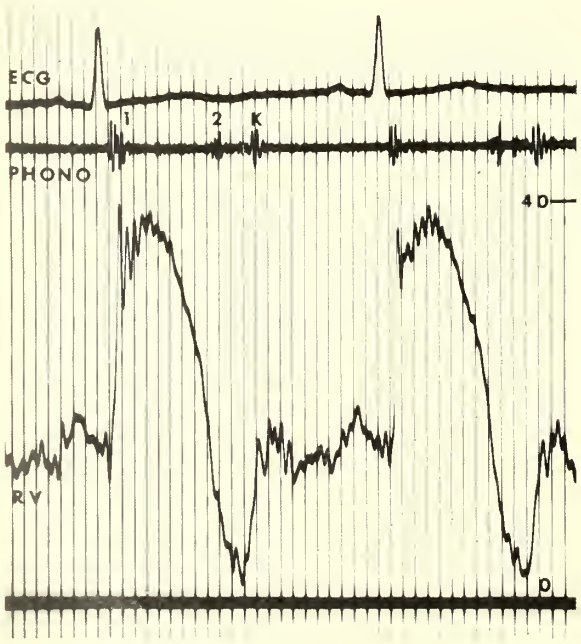

Figure 4.—Right ventricular (RV) pressure in chronic constrictive pericarditis. From top, electrocardiogram (lead II), phonocardiogram and RV pressure. Note the rapid rise of RV pressure in early diastole, reaching a plateau during the remainder of diastole. This rapid pressure rise coincides with the pericardial knock (k) in the phonocardiogram.

The most useful diagnostic procedure for the detection of intrapericardial fluid is an echocardiographic study.[8] This is a bedside procedure which does not require either the insertion of catheters or the injection of dye into the heart. Furthermore, the results of this study are immediately available.

An electrocardiogram is of limited value in the presence of pericardial effusion. With the accumulation of large amounts of fluid there is usually low voltage throughout. In the presence of tamponade electrical alternans may be present. This refers to the simultaneous alternation in electrical amplitude of both P wave and QRS complex. When

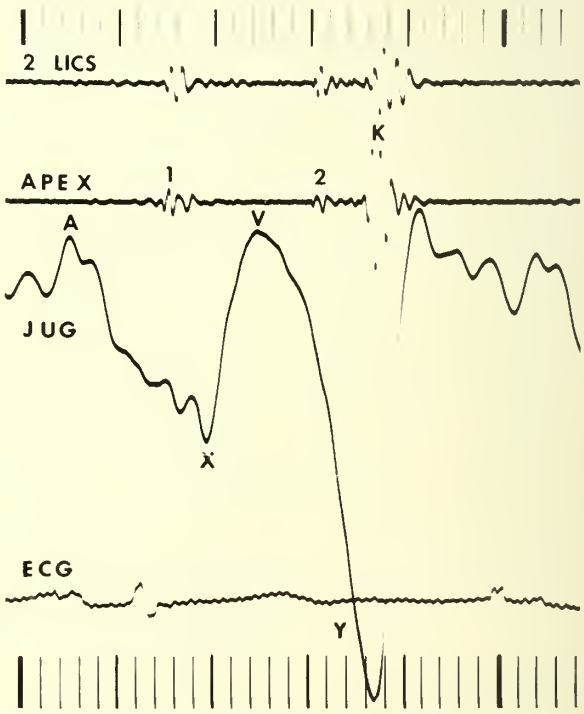

Figure 5.—Jugular venous pressure recording in chronic constrictive pericarditis. From top, phonocardiogram recorded in second left intercostal space (2 LICS), and at apex, jugular venous pressure (JVG) and electrocardiogram. Note the prominent Y descent with an abrupt rise in early diastole.

present, it is virtually pathognomonic of pericardial tamponade. Alternation of only the QRS complex (Figure 3) is highly suggestive of tamponade when persistent and when seen in the appropriate clinical setting. Electrical alternans is thought to be the result of the rotational and pendular motion of the heart suspended in a fluid filled sac.[6]

Constrictive Pericarditis

Constrictive pericarditis is similar to pericardial effusion in that the major hemodynamic deficit results from a restriction of ventricular filling.[4] Unlike pericardial effusion, however, it is due to the presence of a fixed rigid encasement around the ventricles. Early in diastole the ventricular pressure is low and there is a prominent atrioventricular gradient permitting a rapid inflow of blood from the atria. The rigid encasement of the ventricles, however, prevents ventricular expansion so that ventricular pressure soon abruptly rises and reaches a plateau during the remainder of diastole (Figure 4). At this point the pressure in all four cardiac chambers is equal.

On physical examination the jugular venous pressure is elevated and a prominent X descent similar to that seen in effusion may be noted. However, the most striking feature of the venous pulse is the presence of a rapid diastolic collapse, the so-called Y descent (Figure 5). This corresponds to the period of rapid diastolic filling very early in diastole. On auscultation an early diastolic sound similar in timing to the ventricular gallop sound (S3) may be noted. This is referred to as a pericardial knock and occurs as ventricular diastolic pressure is rapidly rising (Figures 4 through 6). On palpation of the precordium a systolic apical retraction and early diastolic expansion may be appreciated (Figure 6). The early diastolic wave occurs coincident with the pericardial knock and with the rapid rise of ventricular diastolic pressure. Pulsus paradoxus may be seen in constrictive pericarditis, but is noted only in approximately a third of cases. In long-standing pericardial constriction chronic atrial fibrillation is commonly present. On x-ray films of the chest the heart is frequently normal in size but may be small or somewhat enlarged. The presence of pericardial calcification is an important diagnostic finding.

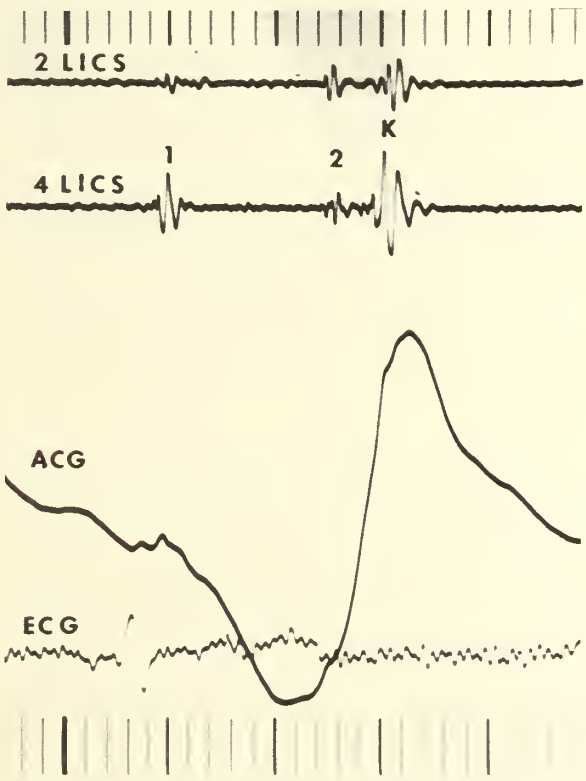

Figure 6.—Apexcardiogram (ACG) in chronic constrictive pericarditis. From top, phonocardiogram recorded in second left intercostal space (2 LICS) and in fourth left intercostal space (4 LICS), apexcardiogram and electrocardiogram. Note the systolic apical retraction and early diastolic bulge in the ACG. The latter coincides with the pericardial knock.

Viral Pericarditis

MILAN FIALA, MD*

VIRAL PERICARDITIS is frequently associated with myocarditis and the term myopericarditis is used to encompass both.[9] Clinical and experimental evidence of viral endocarditis has been presented.[10,11] It has been also suggested that viral or mixed streptococcal and viral valvulitis may lead to chronic valvular damage.[12] Viral pericarditis may be followed by chronic constrictive pericarditis.[13,14]

Viruses which have been associated, by virus isolation or antibody response or both, with heart disease in man include Coxsackie group B (types 1 to 5) and less often group A (types 4 and 16)

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viruses, (enteric cytopathogenic human orphan (ECHO) viruses (types 9 and 22), influenza A and B, mumps, measles, rubella, variola, vaccinia, hepatitis, adenoviruses, Epstein-Barr virus, cytomegalovirus and varicella-zoster virus.[9,15]

Heart disease has been experimentally reproduced in mice with Coxsackie virus A-9 and B3 viruses,[16] and in adult monkeys, with Coxsackie B-4 virus which produced pancarditis, resembling rheumatic heart disease with valvulitis and myocarditis.[11,17] In adult mice, Coxsackie A-9 virus produced benign heart disease. In young mice, Coxsackie B3 virus caused virulent myocarditis with progressive myocardial injury. The severity of experimental virus infections was increased by factors such as exercise, hydrocortisone, undernutrition, alcohol, pregnancy and virulence of the infecting virus.[16]

Viral involvement of the heart may lead to a wide spectrum of clinical illness:[18,19]

- Symptoms of acute pericarditis.
- Chest pain mimicking myocardial infarction.
- Progressive congestive heart failure.
- A nonspecific influenza-like illness with fever, headache, muscle or joint pains and headache.

Relapses may occur, especially in patients presenting initially with symptoms of acute pericarditis. A history of antecedent viral syndrome with fever, headache, muscle pain, pleural effusion or pneumonitis, and absence of recent angina pectoris help to differentiate myopericarditis from coronary heart disease.

Coxsackie B viruses[18,19] have been recognized as the most common viral agents in pericarditis, either by demonstration of antibody rise or by isolation of virus from stool, throat or pericardial fluid. Other viruses have been incriminated usually only serologically. Other known infectious agents and other causes such as chest trauma; toxins; neoplasia; collagen vascular, hormonal and metabolic diseases need to be excluded by appropriate studies. In most cases, a specific cause cannot be, however, identified. In order to understand the cause of idiopathic cases of myopericarditis, it is helpful to remember that in experimental disease in mice, infectious virus is commonly present in excretions and heart tissue only during the incubation period and in the acute stage of the disease.[20] The presence of antibodies to the heart muscle and virus antigen in the heart may be the only remaining trace of virus activity in chronic noninfectious phase.

High prevalence of elevated neutralizing antibodies to Coxsackie group B viruses[21] decreases their diagnostic value. Demonstration of immunoglobulin M (IgM) type-specific antibodies to Coxsackie B viruses may help to establish an etiological diagnosis in those cases of myopericarditis where the usual diagnostic techniques fail.[22]

Patients with viral myopericarditis should be treated with complete bedrest. Mice infected with Coxsackie B viruses which were forced to swim for their life invariably died with enlarged hearts, whereas the heart size remained normal if they were allowed to rest.[23] The use of corticosteroids is controversial. In animal studies, corticosteroids administered during the acute phase of Coxsackie virus infection enhanced virus titers and lesions.[24] In the experience of some clinicians, however, steroids appear to be life-saving in later stages of the disease if the patient is developing heart failure in spite of full bedrest and digitalization.[25]

Tuberculous and Fungal Pericarditis

MATTHEW O. LOCKS, MD*

THERE IS CONSIDERABLE MERIT in including tuberculous pericarditis and fungal pericarditis in a conjoint discussion of these entities since they share many common features when affecting the human host. Both entities have similar pathogenesis, pathological findings, and in many instances, a clinical presentation by history, physical examination, x-ray findings and physiological alterations, that precludes the separation of tuberculous pericarditis from fungal pericarditis. Moreover, both categories of disease are usually accompanied by the development of cutaneous hypersensitivity to the specific infectious agent. Furthermore, the management of tuberculous

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pericarditis and fungal pericarditis, as well as their complications, embodies similar therapeutic principles and techniques. Differences arise mainly in the form of antimicrobial therapy which is dependent on the specific infectious agent, as well as differences in incidence and prognosis of these infections as currently observed.

In general, this form of pericarditis is a chronic, insidious and progressive form of inflammation, making it impossible to document its duration. On occasion, tuberculous and fungal pericarditis present as acute, rapidly progressive purulent pericarditis.[26] The clinical presentation is characterized by the symptoms and signs of pericardial inflammation (precordial chest pain, fever and pericardial friction rub) as well as associated hemodynamic dysfunction. Less frequently, because of the insidious course of this form of pericarditis, only the hemodynamic consequences of the restrictive cardiac defect may be evident (jugular venous distension, hepatic congestion, ascites and peripheral edema). When the pericarditis is associated with concurrent inflammation of contiguous structures within the thorax—which include lesions within the endocardium, myocardium, other mediastinal structures, pleura, lung, chest wall or diaphragm—or if the pericarditis occurs as part of a disseminated infectious process, the clinical presentation will be varied, reflecting the altered morphology and function of the affected organs. With increasing frequency, this form of pericarditis, particularly of fungal origin, appears during the course of a primary disorder, usually neoplastic or lymphomatous, which can obscure the infectious nature of the pericarditis.

Cause

The mycobacterium responsible for tuberculous pericarditis, identified by culture or guinea pig inoculation, has been the human variety, Mycobacterium tuberculosis.[27] Although the various atypical mycobacteria are capable of producing pathologic changes that are indistinguishable from M tuberculosis, their presence in pericardial lesions is unknown. In view of the growing interest and knowledge concerning atypical mycobacteria, it is reasonable to anticipate atypical mycobacteria will be cultured in a patient with tuberculous pericarditis, albeit a remote possibility.

The species of fungi that have been recovered from pericardial lesions are numerous. These can be separated into the pathologic fungi responsible for the systemic mycoses in the otherwise healthy host, and the opportunistic fungi which become invasive as a result of an alteration in the defense mechanisms or bacterial flora of the host. In the former group, Histoplasma capsulatum,[28-30] Coccidioides immitis,[31] cryptococcus,[32] blastomyces,[33] actinomyces[34] and nocardia,[35,36] have been isolated either from the pericardial exudate or from tissue biopsy specimens. In the latter group, candida and aspergillus have been recovered,[37] usually as part of a generalized infection in the immunologically impaired host.

The frequency with which these infectious agents have been associated with pericarditis has increased considerably during the past two decades. Before that time, the most common cause of granulomatous pericarditis was tuberculosis, accounting for 20 percent of all forms of pericarditis.[38,39] With effective tuberculosis control, resulting from increasing efforts in the detection, drug treatment and prevention of tuberculous infection, the incidence of tuberculous pericarditis has been significantly reduced. In those areas of the world where tuberculous infection remains prevalent and less well controlled, tuberculosis remains the most common cause of infectious pericarditis.[41]

Pericarditis due to the pathogenic fungi occurs infrequently and sporadically, constituting approximately 1 percent of all forms of pericarditis. Because of the magnitude of histoplasmosis in the United States, it is not surprising that histoplasmosis is the most common fungal agent responsible for granulomatous pericarditis and constrictive pericarditis, particularly in the great river valleys where histoplasmosis is endemic.[42-44] Likewise, sporadic cases of coccidioidomycosis with pericarditis are recognized primarily in the southwestern portion of the United States and the northern states of Mexico, where this infection is endemic.

Of greater concern is the increasing frequency of pericarditis due to saprophytic fungi, as well as fungi of usually low virulence such as Nocardia asteroides. This can be attributed in large measure to specific therapeutic modalities which have been introduced or used with increasing frequency during the past several decades. These include broad spectrum antibiotics, corticosteroids, cancer chemotherapy and radiation therapy. Colonization of mucous membranes by saprophytic fungi with

subsequent systemic dissemination has been observed in association with use of these therapeutic modalities, frequently in combination. The reactivation of previously stable foci of fungal and mycobacterial infection has also been associated with the prolonged use of immunosuppressive agents. The increased practice of intravenous drug abuse has also contributed to a rising incidence of fungal infection associated with pericarditis.

Pathology

The initial histologic response to an acute tuberculous or fungal infection is a polymorphonuclear leucocytic infiltration. This can progress to frank suppuration with abscess formation. More commonly in tuberculosis, however, the original inflammatory response subsides, with an influx of plasma cells and lymphocytes and the formation of noncascating granulomata. Surrounding these lesions is a fibrotic reaction, with the formation of collagen. Cascation necrosis is a later sign of the granulomatous response and may not appear until many months have elapsed since the initial infection. Calcification and further fibrosis occur after caseation.

The serial histologic responses to fungal infection encompass similar pathologic changes seen with tuberculous infection. Certain fungi, especially Blastomyces and Actinomyces species evoke a persistent suppurative response, with very little granuloma formation, while Histoplasma and Coccidioides species often have pathological changes indistinguishable from those caused by M tuberculosis. It is essential to obtain special stains for acid fast bacilli and fungi on all tissues removed for study, since these organisms are frequently not identified on routine histologic sections alone. Even in the absence of granuloma formation, special stains are essential to identify the etiologic agent.

In tuberculous pericarditis, the administration of antituberculosis chemotherapy for several weeks may be sufficient to significantly reduce or eliminate the organisms in biopsy tissue obtained at that time, so that acid-fast bacilli will not be observed in histologic sections. The granulomatous changes, on the other hand, heal more slowly and can be identified histologically for a protracted period of time while on chemotherapy. For the same reason, culture of the biopsy on appropriate media may successfully yield the infectious agent, despite its absence in histologic section.

Pathogenesis

The portal of entry for M tuberculosis, as well as the majority of the pathogenic fungi, is the respiratory tract. As part of the primary infection, not only is there a lobular pneumonitis within the pulmonary parenchyma, but characteristically there is dissemination through the lymphatic channels to the regional lymph nodes, both in the hilus of the infected lung and in the adjacent mediastinum. Frequently, the supraclavicular nodes are similarly affected. In addition, shortly after the initial infection, there is a generalized dissemination of the infectious agent through the blood stream, establishing secondary foci in many, if not all, body organs.

Most of the secondary foci, either by the lymphogenous or hematogenous dissemination, are clinically inapparent and together with the primary focus undergo spontaneous healing, but still contain viable tubercle bacilli or fungi. For reasons that are not clear, the inflammatory process within certain foci will continue to actively suppurate, caseate, and perforate into adjacent structures. It is primarily this mechanism that results in pericardial infection, namely, the extension of the inflammatory process into the pericardium from a strategically situated caseous hilar or mediastinal lymph node. Hematogenous seeding of the pericardium can occur not only during the initial course of the primary infection, but also as part of a late miliary dissemination, resulting in direct seeding of the pericardium or, more likely, the production of microabscesses in the subjacent myocardium which ultimately rupture into the pericardial space.

The saprophytic, as well as less virulent fungi, obtain access into the body through the mucosa of the body cavities and the gastrointestinal tract. Occasionally there is inoculation of the infectious agent into the skin, with later dissemination. Penetrating wounds of the thorax and surgical procedures on the heart, including pericardiocentesis, create potential pathways for the introduction of the infectious agent into the pericardium. Moreover, with the increasing incidence of intravenous drug abuse with complicating fungal endocarditis and myocarditis, extension of the infection into the pericardial space occurs. Penetration of a tuberculous or fungal abscess of the subphrenic space into the pericardium is conceivable but has not been documented. The appearance of tuberculous pericarditis or fungal

pericarditis following a pulmonary resection for disease due to these infectious agents has been observed.[45]

Diagnosis

In view of the varied clinical spectrum of pericarditis, it is essential to consider mycobacteria and fungi as possible etiologic agents promptly and without exception. Only by recovering the agent in culture, either from the pericardial exudate or identifying it with certainty by culture or histologic section of the pericardium, can a definitive diagnosis be made. Pericardiocentesis and pericardial biopsy by the intercostal or subxiphoid approach has been used for this purpose.[46] The pericardial fluid thus obtained is exudative in character, serous or serosanguinous in appearance, and contains varying numbers of inflammatory cells which reflect the state of inflammation of the pericardial surface. Appropriate cultures of the pericardial fluid for acid-fast bacilli are positive in only 25 percent of the patients with proven tuberculous pericarditis. While a lower yield of positive fungal cultures is obtained in the presence of fungal pericarditis, culture of tissue biopsy specimens will increase the diagnostic yield.

Often other methods must be used to establish a presumptive diagnosis of granulomatous pericarditis so that a reasonable therapeutic regimen can be initiated. These techniques include skin testing with appropriate antigens; serologic tests for fungi, both on pericardial fluid as well as blood serum; cultures of secretions or other areas of exudation or suppuration for acid-fast bacilli and fungi, and selected tissue biopsy for histologic section and culture.

Frequently, the presence of delayed skin test hypersensitivity to a specific microbial antigen indicates the presence of these microorganisms within the subject host, but does not differentiate between past and currently active disease. The conversion of a previously known negative reaction on a skin test to a positive one indicates that the infection by this microorganism was acquired during the interval between the two tests. Conversely, the reversion of a previously known positive reaction on a skin test to a negative one may indicate progressive dissemination by the infectious agent. In the presence of pericarditis due to tuberculosis, histoplasmosis and coccidioidomycosis, the intradermal test is positive to the appropriate antigen with a confidence of greater than 90 percent. Although coccidioidin antigen has greater specificity than other fungal antigens, occasional cross-reactions are seen using fungal antigens, making it necessary to correlate these findings with additional data.[47]

Of greater value in establishing the presumptive diagnosis of a specific fungal infection is the presence of a serological reaction to the fungal antigen.[48] To date, this has been accomplished with considerable confidence in coccidioidomycosis and histoplasmosis. The demonstration of precipitating antibodies in the serum, either to coccidioidin or to histoplasmin, is evidence for a recently acquired infection by the specific fungus. Precipitin antibodies have also been observed to appear during the chronic phase of illness when the infection spreads to a new serosal surface, such as pleura, pericardium or peritoneum. Complement fixing antibodies appear in the serum later in the course of the infection, particularly during the chronic phase of the disease. Rising titers of complement fixing antibodies indicate worsening of infection, while diminishing titers are consistent with control of the infection, making it a useful tool for guidance with specific antifungal chemotherapy.

Additional data supporting the presumptive diagnosis of granulomatous pericarditis is the identification of the infectious agent by culture of histologic technique in other organs or bodily secretions. Accordingly, the presence of acid-fast bacilli or fungi in the smears and cultures of sputum, pleural effusion or blood, or the identification of the microorganism in the lung, lymph node, liver or bone marrow—or in other sites of suppuration, granuloma formation or fistulous tracts—adds considerable support to the probability that this is the agent responsible for the pericarditis. It is important to emphasize that collection and incubation of these specimens under aerobic as well as anaerobic conditions are essential, since certain fungi, such as Actinomyces, grow best under anaerobic conditions.

Treatment

Therapeutic measures used in tuberculous or fungal pericarditis include:

- *General and supportive care.* This includes measures for the management of chest pain and pyrexia, as well as bedrest when cardiac output is impaired. In the presence of an underlying disease during which pericarditis has appeared, management of the primary disease is essential.
- *Control of the hemodynamic complications.*

The presence of cardiac tamponade resulting from a large pericardial effusion is relieved by prompt and adequate pericardiocenteses. During the early stages of effusive pericarditis, repeated pericardiocenteses may be required. If this problem cannot be controlled, corticosteroids should be added to the therapeutic regimen providing appropriate antimicrobial therapy has been started.

• *Pericardial suppuration.* In the event of an aggressive purulent pericarditis due to tuberculous or fungal infection, surgical drainage may be necessary should pericardiocenteses fail to control this problem. Adequate drainage has been achieved by the creation of a pericardial fenestration which is appropriately drained to the exterior.[49]

• *Tuberculous pericarditis.* If tuberculous pericarditis is suspected, albeit on meager clinical data, the prompt institution of antituberculosis chemotherapy, using two effective agents, such as isoniazid and ethambutol, is recommended. The therapeutic effectiveness and the virtual absence of adverse reactions to these drugs when used in recommended dosages,[50,51] balanced against the increased morbidity and significant mortality that result from delay in the treatment of tuberculous pericarditis, justify this approach.

• *Fungal pericarditis.* In the presence of pericarditis due to the common pathogenic fungi, as in histoplasmosis, coccidioidomycosis, cryptococcosis and blastomycosis, the intravenous administration of amphotericin B has been associated with successful management of the infection. In view of the difficulties involved with the administration of amphotericin B, including its frequent adverse effects, a definitive diagnosis or at least a strongly presumptive diagnosis of fungal pericarditis should be made before amphotericin B therapy. For candida infections, 5-fluorocytosine can be used. Penicillin is effective against Actinomyces species, while sulfonamides have been successfully used in nocardia infections. On occasion, the fungal pericarditis has responded satisfactorily to surgical drainage alone, but this is not recommended without specific antifungal chemotherapy.

• *Constrictive pericarditis.* For the patient in whom there is cardiac embarrassment associated with constrictive pericarditis, pericardiectomy must be considered.[52,53] Although this complication may appear relatively early in the course of granulomatous pericarditis, it is more commonly a late manifestation, appearing many months or years after the original infection. Approximately 50 percent of these patients will show pericardial calcification on conventional x-ray views of the heart in the region of the left ventricle. Tomographic studies may be required to better visualize this abnormality. The response to pericardiectomy is generally satisfactory, with improvement of cardiac output immediately after the operative procedure.[54] In certain patients, however, because of impaired contractility of the ventricles, the increased circulatory load which occurs following pericardiectomy cannot be tolerated, so that congestive heart failure rapidly supervenes.[55]

• *Corticosteroids.* The value of the anti-inflammatory action of corticosteroids in various forms of pericarditis has been well documented.[56] For the control of pain of pericardial origin that does not respond to conventional analgesics and the management of cardiac tamponade that cannot be controlled by repeated pericardiocenteses, corticosteroids have a distinct role in the adjunctive therapy of pericarditis. When an appropriate chemotherapeutic program has been instituted in tuberculous pericarditis, corticosteroids do not exert an adverse effect on the control of the infection. Caution should be observed in the administration of protracted corticosteroid therapy when the infectious agent has not been identified or the patient is not receiving specific antimicrobial therapy. A brief course of corticosteroids to achieve reversal of cardiac tamponade may be sufficient to control this problem, pending the institution of additional therapeutic measures.

The role of corticosteroids in preventing the development of constrictive pericarditis is moot. Some studies have suggested a significant reduction in the incidence of constrictive pericarditis since the advent of antituberculous chemotherapy, especially when an effective drug regimen is administered promptly following the recognition of the pericarditis. In general, the use of corticosteroids for this purpose has not been substantiated.

Summary

Tuberculosis and to a lesser degree systemic mycoses are associated with pericarditis. The incidence of tuberculous pericarditis, both in its effusive and constrictive forms, has been reduced with the control of tuberculosis since the advent of specific antituberculosis chemotherapy. Although tuberculous or fungal pericarditis is usually an indolent and insidiously progressive disease, it can present as an acute suppurative pericarditis.

Every reasonable effort should be made to identify the etiologic agent so that an appropriate therapeutic program can be initiated. Since the previously high mortality of tuberculous pericarditis has been remarkably reduced by the early administration of an appropriate drug regimen, this practice is recommended whenever tuberculous pericarditis is suspected. It is important to establish the diagnosis of a specific fungal pericarditis because of differences in antimicrobial chemotherapy. The indications for pericardiocentesis, corticosteroids, surgical drainage and pericardiectomy in the management of this form of pericarditis have been reviewed.

Bacterial Pericarditis

THOMAS T. YOSHIKAWA, MD*

THE CLINICAL signs and symptoms of bacterial (purulent) pericarditis are similar to those of the other forms of pericarditis except that the patients are usually more toxic and ill with rapidly changing hemodynamic abnormalities.

Bacterial pericarditis is an old disease first described in an animal by Galen in the first century and subsequently described in humans approximately a thousand years ago. The incidence of bacterial pericarditis from autopsy series before the antibiotic era was about 40 percent of all pericarditis;[57] subsequent to the antibiotic era the incidence has decreased to 10 to 20 percent.[57] Additionally, autopsy series showed that purulent pericarditis before 1945 was responsible for approximately 1 percent of all deaths.[57] Since 1945, however, the figure has been less than 1 percent.

The pathogenesis of bacterial pericarditis occurs through several mechanisms:

- *Contiguous spread from an adjacent pleuropulmonary infection.* Before the antibiotic era, most cases of purulent pericarditis were due to the pneumococci and this was invariably associated with pneumonia or empyema or both. The postulated pathophysiology has been that the adjacent pleuropulmonary infection may cause an inflammatory response in the pericardium with migration of neutrophils and eventual deposition of fibrin.[26,58,59] It has not been clear whether bacteria migrate directly from the lung tissue itself or there is subsequent bacteremia and invasion of the pericardial sac.
- *The hematogenous spread of bacteria from a distant focus to the pericardium.* Staphylococcal osteomyelitis is a common cause of purulent pericarditis and the pathogenesis is probably via hematogenous spread of the bacteria to pericardium. The exact mechanism is unknown. Animal experiments[60] suggest that an initial myocarditis or myocardial abscess develops. Bacteria then migrate (or rupture from the abscess) into the pericardium to form purulent pericarditis.
- *Direct inoculation of bacteria into the pericardial sac.* This may result from penetrating wounds to the pericardium or occur as a result of cardiac surgery.[57] There have been reports of bacterial pericarditis secondary to infective endocarditis.[61-63] Associated myocarditis with myocardial abscess formation probably permit migration of bacteria to the pericardial space.

The incidence of particular types of bacteria in purulent pericarditis is difficult to assess since most series include only a few case reports. However, a review of the world's literature up to 1959[26] of all cases of purulent pericarditis suggested staphylococci, pneumococci and streptococci as the predominant organisms. There were a moderate number of meningococci reported; since that report, the incidence has increased. In children under the age of two years, the cause of purulent pericarditis is similar to that in adults with staphylococci and pneumococci predominating, but Hemophilus influenza is also a common agent.[64] Hemophilus influenza should always be considered in the pediatric age group. Salmonella species may also cause bacterial pericarditis.[65] Most have been nontyphosal types with Salmonella typhimurium being the most common strain.

Pneumococcal pericarditis was the most common cause of purulent pericarditis before the antibiotic era. However, a recent review by Kauffman and coworkers[59] indicates that there have only been 15 cases of pneumococcal pericarditis reported since 1945. This is probably a reflection of penicillin therapy. Kauffman's group included five cases of their own in this report and it is in-

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teresting that two of their patients had a history of chronic alcoholism and one patient had hypogammaglobulinemia. The three patients that did recover were diagnosed antemortem and the two who died were diagnosed postmortem. Most series indicate that the antemortem clinical diagnosis of bacterial pericarditis occurs 10 to 20 percent of the time, and before the antibiotic era the mortality was essentially 100 percent. In the same report by Kauffman's group, the cumulated cases of pneumococcal pericarditis from other series again showed the high association with pneumonia and empyema. Therefore, pericarditis should be considered a possible complication in patients with pneumococcal pneumonia and empyema.

In staphylococcal pericarditis, hematogenous spread from a distant foci is very common except in children where staphylococcal pericarditis is more commonly associated with pulmonary infection. Osteomyelitis and peripheral skin infections have been the most common sources of bacteremia. In terms of mortality, staphylococcal pericarditis has the worst prognosis.

Meningococcal pericarditis appears to be increasing in frequency despite the availability of antibiotics.[66] Meningococcal pericarditis is almost always associated with meningitis or meningococcemia or both. To my knowledge, there have been only seven reported cases of nonmeningitic meningococcal pericarditis reported in the literature.* Two different pathogenic mechanisms may be involved in meningococcal pericarditis. One type of pericarditis is seen early in meningococcal infections when the patient is acutely ill and probably results from direct bacterial invasion of pericardium or hematogenous spread with an associated myocarditis. There is also a late form of meningococcal pericarditis in which pericarditis develops a week or more after antibiotic therapy. The pathogenesis may be either an immunologic or nonimmunologic response to meningococcal endotoxin released from bacterial cells.* Fever, pleural effusion, arthritis or arthralgia are seen in many of these patients. The pericardial fluid and other lesions have been cultured with no bacteria recovered. It is important to remember this syndrome because most of these patients will respond to anti-inflammatory agents such as acetylsalicylic acid or steroids and needle aspiration.

As far as complications of bacterial pericarditis are concerned, it is important to emphasize that cardiac tamponade is the cause of death for most patients with this disease mainly because of failure in making an early diagnosis. Congestive heart failure from associated myocarditis may be a major problem. Constrictive pericarditis is relatively uncommon in bacterial pericarditis.[26,57,64] In patients with purulent pericarditis who have been followed clinically, constrictive pericarditis has failed to develop, as opposed to patients who have tuberculous pericarditis—in whom this complication not uncommonly develops.

In the management of bacterial pericarditis, the single most important factor is a high index of suspicion. Only 10 to 20 percent of these cases are diagnosed antemortem. Because one of the pathogenic mechanisms is bacteremia, peripheral foci of infection must be looked for and appropriate cultures obtained including blood. Evidence for associated pleuropulmonary infection should be investigated and appropriate cultures taken. Careful cardiac and hemodynamic evaluation should be made. Pericardiocentesis should be carried out in suspected cases of purulent pericarditis. The etiological diagnosis will not be made unless some pericardial fluid is examined. Once the fluid is obtained, Gram and acid-fast stains should be made immediately and the fluid cultured for bacteria, fungi, virus and Myobacterium tuberculosis. The characteristics of the aspirated fluid should be noted and examinations for cell count, differential, glucose and protein obtained.

The antibiotics most frequently used until the cause is established are penicillin or methicillin or both, administered intravenously in large doses. In the pediatric age group, ampicillin instead of penicillin should be used if Hemophilus influenza is thought to be the cause.

Drainage is extremely important. Repeated pericardiocentesis using a percutaneous approach should be used if reaccumulation occurs. If adequate drainage cannot be achieved, then an open surgical drainage should be instituted. If, beyond that, drainage becomes a problem because of tamponade, pericardiectomy may be indicated. With the institution of systemic antibiotics and adequate drainage, survival rates of 50 to 75 percent can be achieved.[26,57] However, improvement on these figures can only be achieved with early recognition of bacterial pericarditis and prompt initiation of therapy.

*Unpublished data submitted for publication.

Parasitic Causes of Pericarditis

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ALTHOUGH MYOCARDITIS is frequent in African trypanosomiasis and American trypanosomiasis (Chagas' disease), involvement of the heart is an uncommon association with other parasitic diseases and pericarditis is even more rare.

Pericardial effusions containing larvae have been described in severe infections with Trichinella spiralis, but the myocarditis in these patients overshadows the pericardial involvement. Toxoplasmosis has been reported as a cause of pericarditis.[67,68] Usually, the diagnosis has been made by serologic methods. One patient with a serologic response diagnostic of toxoplasmosis had pericarditis with progressive pericardial constriction.[69]

Microfilariae have been found in the fluid aspirated from a pericardial effusion,[70] and constrictive pericarditis has been described in a patient in whom a pericardial effusion associated with filariasis developed.[71]

Pericarditis is an uncommon but well described complication of amebic liver abscess. In almost all patients, the abscess has been located in the left lobe of the liver, but there have been rare instances in which abscesses of the right lobe have extended into the pericardial sac.[72]

Initially, the pericardial involvement may be a serous or serosanguinous effusion (presuppurative stage), but this progresses to a purulent effusion when there is direct communication between the liver abscess and the pericardial cavity (suppurative stage). Although many patients will have a history of travel in areas of the world where amebiasis is common, it should be emphasized that amebic liver abscess and pericarditis occur sporadically in temperate areas, including the United States. The clinical manifestations usually begin with signs and symptoms of a left lobe liver abscess. Epigastric or low retrosternal pain, nausea, vomiting, left shoulder pain, cough, dyspnea, low grade fever, weight loss and tender hepatomegaly are common findings.[73,74] A few patients present solely with symptoms of pericarditis. Pericardial involvement is frequently suggested by rapid progression of symptoms and the appearance of signs of pericardial tamponade. Enlargement of the cardiac outline and the "water bottle" configuration of pericardial effusion are commonly seen on chest roentgenograms. Electrocardiography shows changes seen in other forms of pericarditis. Low voltage is also frequently present.

Patients with amebic pericarditis who are misdiagnosed or receive inadequate treatment usually die of pericardial tamponade. When adequate therapy is initiated early, two thirds of the patients may be expected to survive.[74] A few patients have developed constrictive pericarditis following resolution of the acute problem and in spite of adequate antiamebic therapy.

Diagnosis of amebic pericarditis is dependent on detecting the underlying liver abscess by hepatic scan or echogram. Results of serologic tests for amebiasis have been positive in more than 90 percent of patients with hepatic amebiasis. Examination of material aspirated from the liver or pericardium may reveal trophozoites of Entamoeba histolytica. Fecal examination should be carried out but findings are usually negative for amebae.

Immediate treatment is directed toward relieving or preventing pericardial tamponade. This may be done by percutaneous needle aspiration, repeated as frequently as necessary,[74] or by the creation of a subxiphoid pericardial window under local anesthesia.[75] Specific antiamebic therapy should be instituted immediately. Metronidazole has become the drug of choice for the treatment of hepatic amebiasis; however, doubt has been raised about its efficacy in patients with pericardial involvement.[72] Metronidazole attains a high concentration in the liver, but not in the myocardium. Until more information is available, treatment of amebic pericarditis should consist of a combination of chloroquine phosphate 250 mg four times a day for two days then twice a day for 28 days *and* emetine hydrochloride 1 mg per kg of body weight with 65 mg maximum given intramuscularly daily for 10 days (alternate dihydroemetine dihydrochloride 1 to 1.5 mg per kg of body weight for ten days; maximum total dose 1 gram). A luminal amebicide such as diiodohydroxyquin 650 mg three times a day for 21 days will reduce the likelihood of a persistent, undetectable enteric infection with E histolytica.

Patients should be followed closely after treatment for signs of constrictive pericarditis.

Hydatid disease is caused by the ingestion of

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eggs of the tapeworm Echinococcus granulosus. The source of the eggs is usually dog feces, but other carnivores are capable of harboring the adult tapeworm. The ingested eggs hatch in the intestine, and the liberated embryos burrow through the intestinal mucosa and enter the vasculature. They are carried to various tissues where they develop into the larval form, the hydatid cyst. The embryos must pass the filters of the liver and lungs before reaching the blood supply of the myocardium. Therefore, it is not surprising that the majority of patients with hydatid disease have cysts localized to the liver or lungs. Myocardial involvement is seen in only 0.3 to 3.3 percent of cases of hydatid disease.[76]

Pericardial involvement occurs when the cyst in the myocardium ruptures into the pericardial sac. This event frequently is not clinically detectable, or it may lead to a fibrinous or fibrinopurulent pericarditis.[76] In addition, larval tissue may produce secondary cysts. As the secondary cysts enlarge, they may cause a pericardial reaction and the signs and symptoms of constrictive pericarditis.[77] An acute pericarditis has been reported in association with allergic manifestations including anaphylaxis.[78,79] This condition may progress to massive pericardial[80] effusion with tamponade. A fibrotic reaction of the epicardium which impaired cardiac function and mimicked constrictive pericarditis has also been reported.[80]

The diagnosis of echinococcosis may be suspected in patients who have lived in endemic areas. There may be roentgenographic features of unusual bulges in the cardiac silhouette, intracardiac or pericardial calcifications and, infrequently, the finding of hydatid cysts in the liver or lung. The electrocardiogram may show diminished R waves or the presence of Q waves over the area of the intracardiac cyst. Deep T wave inversion may also be seen in the affected precordial leads.

Skin testing with hydatid fluid (Casoni test) may show reactivity, but false negatives are not uncommon. Serologic tests may be helpful but a negative result does not rule out hydatid disease.

Surgical removal of the cysts is the only effective treatment. Myocardial cysts may be technically very difficult to excise depending upon their location. It is essential that remnants of larval tissue be destroyed or secondary cysts may develop. Formalin, alcohol and 33 percent sodium chloride solution have been used to sterilize cyst cavities. Because of the nature of the myocardium, the concentrated salt solution is considered the agent of choice.[77] The use of formalin in the pericardial sac may cause a chemical constrictive pericarditis.

Patients who have had pericardial or myocardial cysts removed require careful follow-up. Electrocardiographic changes may indicate the development of secondary cysts and the need for reoperation.

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Refer to: The enigma of periarteritis nodosa—Medical Staff Conference, University of California, San Francisco. West J Med 122:310-315, Apr 1975

The Enigma of Periarteritis Nodosa

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Assistant Professor of Medicine, and H. David Watts, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, CA 94143.

DR. WILLIAMS:* *It has been traditional for the chief medical residents at San Francisco General Hospital to present a medical grand rounds session at the conclusion of their experience, and today we will hold to this tradition. Dr. Kenneth Fye has had a long interest in rheumatology and will review today the enigma of periarteritis nodosa.*

DR. FYE:† In 1755 Michaelis and Matanni published the first pathologic description of a patient who died with what appeared to be a diffuse vasculitis. Almost 100 years later, in 1852, von Rokitansky published the first detailed necropsy report, but it was not until 1866 that Kussmaul and Maier recognized the disease as a clinical syndrome and called it periarteritis nodosa. Since then approximately 1,000 cases have been reported in the literature.

I shall begin by presenting an illustrative case, and follow with some comments about the entity of periarteritis nodosa and the frustrations arising from its treatment.

Report of a Case

The patient is a 38-year-old white man who presented at San Francisco General Hospital on January 31, 1974 with right lower quadrant and right flank pain of one day's duration. He had noted mild malaise and lethargy for approximately one month but denied fever, chills, arthralgias, myalgias, rashes, hematuria or diarrhea. The patient had no allergies or history of major illnesses. Although he reported that he did not use alcohol or medicines, the patient had smoked up to four packages of cigarettes a day since the age of nine. Review of systems showed a six-month history of dyspnea on exertion and mild productive cough.

On physical examination the patient was asthenic and in moderate distress. Blood pressure was 140/75 mm of mercury with a pulse of 100, a respiratory rate of 25 and a temperature of 97.2°F (36.2°C). The head, eyes, ears, nose and throat were normal. Examination of the chest showed an increased anteroposterior diameter with hyperresonance to percussion. A prolonged expiratory phase and use of accessory muscles of respiration were noted. No rales or wheezes were auscultated. Results of the cardiac examination were normal. There was no abdominal organomegaly. There was, however, right lower quadrant abdominal tenderness to palpation and rebound, associated with moderate abdominal guarding. No abnormalities of the genitourinary system, skin, muscle or neurological system were found. Stool guaiac was negative.

The hematocrit was 31 percent and leukocyte

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count was 30,000 per cu mm. Results of urinalysis showed 10 to 15 leukocytes per high power field. No red blood cells or red blood cell casts were seen. An electrocardiogram showed a sinus tachycardia, and an x-ray film of the chest showed bibasilar fibrosis with apical bullous disease.

On the day after admission, an exploratory laparotomy was carried out and a large right-sided retroperitoneal hematoma was noted. Attempts to define a bleeding site during operation were unsuccessful. Visceral arteriographic studies done postoperatively showed multiple aneurysmal dilatations of the small to medium sized branches of the celiac, superior mesenteric and right renal arteries. Also noted was lateral displacement of a branch of the right renal capsular artery. These findings were felt to be consistent with periarteritis nodosa and a subcapsular renal hemorrhage leading to a retroperitoneal hematoma. After the operation the patient's hematocrit rose to 38 percent, and the leukocyte count fell to 6,800. Eosinophilia did not develop. Results of urinalysis remained within normal limits. Findings from testicular biopsy, done in an attempt to verify the diagnosis of periarteritis nodosa, were normal. Postoperatively, a blood pressure of 200/120 mm of mercury developed. Renal vein renin studies showed notably elevated levels of renin from the right renal vein suggesting that the hypertension was renovascular in origin. Hypertension was easily controlled with thiazide diuretics and alpha methyldopa. The patient has remained asymptomatic since discharge. The erythrocyte sedimentation rate, however, has remained elevated at 40 mm per hour.

Discussion

It seems likely that, despite the negative findings on testicular biopsy, this patient suffers from periarteritis nodosa. Kussmaul and Maier described periarteritis nodosa as a progressive, recurrent, necrotizing, inflammatory panarteritis affecting chiefly small to medium sized arteries. As reported cases of periarteritis nodosa began to accumulate, a certain amount of confusion developed as to the characteristic clinical and pathological abnormalities. This confusion arose because (1) the lesions in pariarteritis undergo a histologic evolution, (2) the clinical manifestations of periarteritis are protean in nature and depend on the particular organ system involved and (3) attempts to define a specific etiologic agent have been frustrated. Therefore, to subclassify the disease by organ system involvement, length of survival, or histologic appearance have generally added to the confusion.

In 1953, Pearl Zeek[1] described five types of arteritis. Temporal, or giant cell arteritis, and rheumatoid vasculitis are important to distinguish, since each of these diagnoses carries a significant therapeutic implication. However, the other three categories likely represent different presentations of the same disease. If, for example, a patient with periarteritis nodosa had overwhelming disease—particularly with lung involvement—and died within a few weeks to months of the onset of the disease, most of the arterial lesions would be at approximately the same stage in their histologic evolution and would appear similar; classically, this disease would be called hypersensitivity angiitis. If, however, the patient survived for several months—and therefore there was time for several generations of vascular lesions with different histologic features to develop—and the gastrointestinal tract became involved, the diagnosis would be that of classic periarteritis nodosa. And lastly, if the patient survived for many months to years, granuloma and giant cell formation would occur, and the disease would likely be called allergic granulomatous angiitis.

The schema outlined by Rose and Spencer[2] is less cumbersome. Here the disease is defined simply as a focal, segmental, necrotic inflammatory process usually involving small muscular arteries. They do find it clinically useful to categorize the disease as to the presence or absence of lung involvement.

The histologic phases in the evolution of a given lesion were best described by Arkin in 1930[3] and restated by Churg and Strauss in 1951.[4] In the acute phase can be seen fibrohyaline degeneration of the media of the involved vessel. These changes are closely followed by an acute necrotizing perivascular infiltration with polymorphonuclear leukocytes, eosinophils, lymphocytes and plasma cells. With destruction of the vessel wall, aneurysm formation or hemorrhage or both may occur. Granulation tissue with fibroblastic proliferation may next develop; at this stage the vessel lumen may be occluded by intimal proliferation. The lesion finally progresses to reparative fibrosis and scar tissue formation, with or without luminal obliteration. Unfortunately, these histological findings are not absolutely diagnostic, and cannot be distinguished from those found in rheumatoid vasculitis and systemic lupus erythematosus, and

from the lesions associated with subacute bacterial endocarditis. These vascular lesions may occur in virtually every organ in body, the commonest organs involved being the kidney, heart, liver and gastrointestinal tract (Table 1). It is of note that the lungs are involved at autopsy in 24 percent of cases and that the testes, the most common site of blind biopsy, are involved in only 19 percent.[5]

Periarteritis presents with protean manifestations that depend upon the particular organ systems involved (Table 2). The male to female ratio is 2 to 1. However, lung involvement occurs equally in both sexes. The five-year mortality of the disease is 90 percent, with an average duration of survival of 8.6 months.[7] Approximately 70 to 80 percent of patients have complaints of general symptoms of fever, malaise, myalgias and arthralgias.[5,8] Renal involvement, typically glomerulonephritis, develops in 60 percent of cases, and in 26 percent of those patients with renal involvement, terminal azotemia develops later.

Hypertension, presumably renal in origin, develops in approximately 50 percent of patients with periarteritis nodosa.[2,6,7] Gastrointestinal symptoms of nausea, vomiting, diarrhea and abdominal pain are seen in 60 percent.[5,7] Well-known gastrointestinal complications include bowel infarction, hemorrhagic infarction of the pancreas, granulomatous hepatitis and even liver infarction.[5,7] In 55 percent of cases, signs of cardiac involvement are seen, including congestive heart failure, arrhythmias and heart block.[5] Peripheral neuropathies leading to paresthesias, anaesthesia and muscle atrophy have been described in about half of reported cases.[5,7,15] Although only 24 percent of patients have pulmonary involvement at autopsy, some 47 percent of patients have respiratory complaints, including cough, dyspnea, chest pain or asthma. Pneumonia develops as a terminal event in 39 percent of patients. Skin manifestations, including petechiae, purpura, infarction, neurodermatitis and urticaria occur 25 to 35 percent of the time; however, palpable subcutaneous nodules are found in only 16 percent of patients.[5]

There is no specific laboratory test diagnostic of active periarteritis nodosa, though many laboratory abnormalities consistent with active inflammatory disease do occur (Table 3). In 98 percent of patients there is an elevated erythrocyte sedimentation rate (ESR). Leukocytosis, often up to 20,000 to 40,000 leukocytes per cu mm, is found in 75 percent of patients. In 70 percent of patients, findings on urinalysis are abnormal; these findings range from isolated proteinuria to active urinary sediment with leukocytes, red cells and red cell casts. An interesting finding is the frequent occurrence of thrombocytosis greater than 500,000 per cu mm. Eosinophilia, greater than 1,500 per cu mm, is seen in only 19 to 30 percent of patients without lung involvement[5,6] but occurs in 70 percent of patients with lung disease.[6,8] Electrocardiographic (EKG) abnormalities, including heart blocks, conduction disturbances and nonspecific ST-T wave changes, are seen in 64 percent of cases. In addition, any one of a

TABLE 1.—*Organ Involvement with Polyarteritis from Autopsy Reports in the Literature (175 cases)**

Organ	*Percent*	*Organ*	*Percent*
Kidney	85	Peripheral nerves	27
Heart	76	Mesenteric vessels	25
Liver	66	Lungs	24
GI Tract	51	Skin	20
Skeletal muscle	39	CNS	19
Pancreas	35	Testes	19
Spleen	34		

*From Nuzum and Nuzum.[5]

TABLE 2.—*Clinical Signs and Symptoms of Periarteritis Nodosa*

	Percent of Patients		
Manifestations	*Nuzum and Nuzum*[5]	*Frohnert and Sheps*[15]	*Mowrey and Lundberg*[7]
General Systemic	81	76	68
Gastrointestinal	62	14	48
Cardiac	55	10	..
Peripheral Neuropathic	54	55	42
Pulmonary	47	38	36
Cutaneous	55	58	25
Renal			
Hypertension	54	21	58
Azotemia	26	25	27
Abnormal urinalysis	71	69	67

TABLE 3.—*Laboratory Abnormalities Seen in Periarteritis Nodosa*

	Percent of Patients		
Abnormality	*Nuzum and Nuzum*[5]	*Frohnert and Sheps*[15]	*Mowrey and Lundberg*[7]
Elevated erythrocyte sedimentation rate	98	99	..
Leukocytosis	74	63	72
Abnormal urinalysis	71	75	64
Eosinophilia	19	46	18
Abnormal electrocardiographic findings	64	..	..

number of abnormal findings on immunological laboratory tests—including a false-positive Venereal Disease Research Laboratories (VDRL) test, and for rheumatoid factor, hyperglobulinemia, macroglobulinemia and cryoglobulinemia—may be obtained in a given patient. The serum complement is normal or elevated.

Given the protean clinical manifestations of the disease and the nonspecific laboratory abnormalities, it is not surprising that the diagnosis of periarteritis nodosa can be extremely difficult. Even though they are nonspecific, and therefore nondiagnostic, we must depend upon the clinical features and the laboratory data to suggest the diagnosis. Biopsy of involved tissue, particularly muscle, skin or subcutaneous nodule, offers the most definitive diagnostic method. Most authors, however, report that only 20 to 35 percent of ante mortem biopsy results are diagnostic, even when specimens are taken from patients who at autopsy prove to have periarteritis nodosa.[5,6,9] The testicles, a common site for blind biopsy, have diagnostic lesions at autopsy in only 19 percent of cases.[5] In addition, many organs frequently involved, such as the liver or kidneys, tend to show nonspecific histological changes that are not diagnostic.

Recently, angiography has been used in the diagnosis of periarteritis nodosa. Aneurysmal dilatation of arteries 1 to 5 mm in diameter in the hepatic, gastrointestinal, renal and perhaps the cerebral circulation are considered pathognomonic of periarteritis nodosa.[10,11] Some authors have found these aneurysms in up to 80 percent of patients.[11] Unfortunately, the absence of aneurysms does not rule out the diagnosis, since aneurysms have been shown to disappear with remission of the disease, and even in the best of series false-negative angiograms occur in 20 to 40 percent of cases. Despite the incidence of false-negative studies, at present visceral angiography appears to offer the best hope of definitive diagnosis in patients who do not have muscle, skin or testicular involvement and in whom we would otherwise have to depend upon blind biopsy for the diagnosis.

The accepted therapy of periarteritis nodosa is high dose corticosteroid administration, usually prednisone, 60 to 80 mg per day, with careful clinical and laboratory follow-up to determine when it is proper to decrease the dose. Steroids are usually administered for months to years. What has been the actual medical experience with these drugs in the treatment of periarteritis nodosa, and how effective are they?

The initial reports of therapeutic attempts with corticosteroids were single case reports, in which the steroids often had little effect on the clinical course of the disease.[13,14] Following those inauspicious beginnings, steroids found widespread use in the treatment of periarteritis nodosa. Only after steroids had become the accepted medical therapy were clinical studies set up to evaluate their effectiveness. One of the biggest and most often quoted clinical studies is the retrospective Mayo Clinic study published by Frohnert and Sheps.[15] They found a 48-percent, five-year survival in 110 patients treated with steroids and a 13-percent, five-year survival in 20 untreated control patients. However, in nine of their controls the disease was undiagnosed until autopsy. Obviously there is no way to control the undiagnosed cases that did not come to autopsy. Eight of the control patients had, in fact, received glucocorticoids before their referral to the Mayo Clinic. It is, therefore, difficult to make a valid comparison of the difference in mortality between the treated and the untreated groups.

In 1957 Geoffrey Rose published the initial results of a study then being done by the Collagen Disease and Hypersensitivity Panel of the Medical Research Council of Great Britain.[16] He reported that in the absence of lung involvement, eight of the 12 patients treated with adrenocorticotropic hormone (ACTH) or corticosteroids survived for more than six months as compared with three of 54 in the untreated group. Only one of eight treated patients with lung involvement survived for six months, and all of the 24 untreated patients with lung involvement died within that time. However, in most of the control patients in this study the disease also was diagnosed only at autopsy. The author recognized this problem and collected 20 cases in whom the diagnosis was made during life, by biopsy, before the steroid era. Of these 20 patients, none of whom received steroid therapy, six survived for periods up to 16 years. This survival rate compares favorably with the 45-percent, six-month survival among the 20 patients treated with corticosteroids during the study period.

The final report of the Medical Research Council appeared in 1960 and indicated a five-year survival of 40 percent among 21 treated patients and 39 percent among 19 nontreated patients.[16] If we examine the data after three years

TABLE 4.—*Survival of Treated Versus Untreated Patients from the Study by the Medical Research Council*[16]

Interval from Biopsy (months)	*Number Alive*		*Percent Alive*	
	Treated	*Untreated*	*Treated*	*Untreated*
0*	21 (20)	19 (11)	100 (100)	100 (100)
12	15 (16)	7 (7)	71 (80)	37 (64)
36	13 (12)	7 (7)	62 (60)	37 (64)
60†	2/5 (1/4)	7/18 (7/10)	40 (25)	39 (70)

*Numbers in parentheses are patients *without* hypertension.
†Numbers in the denominator indicate patients available for follow-up at five years.

of follow-up we find that 62 percent of the treated patients were alive after three years, while only 37 percent of the nontreated patients survived. However, the controls in this study were collected retrospectively and were not randomly chosen concurrent patients. Hypertension was present in eight of the controls at the outset of the study. This weights survival statistics heavily in favor of the treated group. When the patients with hypertension are excluded, the three-year survival is 60 percent for the treated and 64 percent for the untreated group. In addition, in five of the 21 treated patients there developed what the authors considered to be complications of glucocorticoid therapy. These complications included a peptic ulcer that perforated in one patient, de novo peptic ulcers in two patients and osteoporosis and multiple fractures of the spine and ribs in two patients.

Survival among treated patients after 12 months of follow-up was improved even with exclusion of the hypertensive patients (64 percent survival among nontreated and 80 percent survival among treated patients). Therefore, there appeared to be a definite short-term benefit from the use of glucocorticoids (Table 4).

Despite the ambiguities we have just discussed, corticosteroids are now the accepted treatment for this disorder. But for the sake of argument, consider a hypothetical case: A 28-year-old man has a six-month history of myalgias, arthralgias, asthma, leukocytosis, hematuria, elevated sedimentation rate and positive findings on muscle and testicular biopsies of vasculitis of small muscular arteries. The diagnosis would clearly be periarteritis nodosa. Now simply add to the history that sinusitis and rhinorrhea were present for a month before admission. The diagnosis becomes Wegener's granulomatosis and the preferred treatment is immunosuppression, for the response of Wegener's granulomatosis to immunosuppressive therapy has been well documented. Novack and Pearson[17] and Fauci and associates[18] reported on a combined experience with 13 patients treated with cyclophosphamide. Among their patients there were nine complete remissions, two partial remissions, one patient with no active disease but residual azotemia and one patient in whom active local glomerulonephritis developed during therapy. This experience has been confirmed by other workers with other immunosuppressive agents. Although periarteritis and Wegener's may not be the same disease, they both affect small arteries and arterioles, they often affect the same organs and they can present with an identical histological appearance. Furthermore, the precedent for the use of immunosuppressive agents in the therapy of periarteritis nodosa has been set. Melam and Patterson[19] described a 17-year-old boy with periarteritis nodosa who had received up to 80 mg of prednisone a day without response. After being started on azathioprine he went into a remission which lasted for at least eleven months. Because periarteritis has such a high mortality, it is difficult to justify morally a controlled treatment-placebo study. However, given the equivocal response of patients with periarteritis to steroid therapy, it would seem ethically acceptable to set up a controlled study comparing the effectiveness of corticosteroids and immunosuppressive agents.

In summary, we can define periarteritis nodosa as a diffuse vasculitis affecting small to medium sized arteries. The clinical and laboratory abnormalities that characterize the disease have been well described. However, attempts to define an etiologic agent have met with frustration since the time of Kussmaul and Maier. Consequently, the results of our therapeutic attempts have been less than dramatic. And finally, since the data supporting the effectiveness of glucocorticosteroids is weak at best, the possible use of immunosuppressive agents in the therapy of periarteritis nodosa deserves exploration.

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Important Advances in Clinical Medicine

Epitomes of Progress—Radiology

The Scientific Board of the California Medical Association presents the following inventory of items of progress in Radiology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in Radiology which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Radiology of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, California Medical Association, 731 Market St., San Francisco, CA 94103

Computed Cerebral Tomography

COMPUTED TOMOGRAPHY (CT) is a new radiologic technique which was introduced in England in 1970. The first units to be installed in California have been operational for only a few months; by the latter part of 1974 there were six functioning scanners in the state. Using cerebral computed tomography, we are able for the first time to obtain precise information about the brain using a noninvasive procedure. The use of this technique will have a profound effect upon the neurosciences.

The technique of computed tomography is quite unlike that used in conventional radiography—a narrow beam of x-rays is passed through the head and is detected by sensing devices which always remain in alignment with the x-ray source. Both the x-ray tube and the detectors traverse the patient's head linearly, taking multiple readings of transmission. The x-ray scanning unit is then rotated around the head and the process is repeated: 28,800 readings are obtained from 180 traverses. These readings are then processed by a small computer which calculates absorption values, thus providing a measure of the density of numerous small regions of tissue within a "slice" of the head. The system yields much more information on brain tissue than does conventional x-ray examination and can distinguish small variations in tissue density. Irradiation of the skin is confined to the narrow band of the "slice" and the integral dose from a single complete scan is likely to be less than that from a single roentgenogram of the skull.

From the calculations done by the computer, a picture is built up in the form of a matrix of many points. The matrix is shown on a cathode ray tube viewing unit and is also printed out numerically. The data may also be stored on magnetic tape for subsequent analysis or regeneration of the cathode ray tube display. The latter is readily photographed by an attached camera system. During

an examination by CT the patient is required to remain immobile for several minutes. Restless patients and children may require sedation to minimize movement. With present equipment, 12 to 15 patients can be examined in a ten-hour day, but with anticipated technical improvements, this patient volume may be increased.

The ultimate resolution of the instrument is determined by the physical characteristics; with the 80 by 80 matrix that has been standard until just recently, the computer calculates the results in a three mm square with a thickness that can be varied from 8 to 13 mm, with 13 mm being the accepted standard. The new high resolution option, recently available, has a 160 by 160 matrix so that the computer will be looking at squares half the size of the original. There are other improvements included with the high resolution option which it is hoped will contribute to lessening the rate of error. A modification of the technique of examination which will contribute to a reduction in the error rate is the use of contrast enhancement; this is proving to be especially helpful in certain meningiomas, smaller acoustic neurinomas, metastasis and arterial venous malformation. Other factors which limit resolution are (1) motion and (2) physical factors at the skull base, in the posterior fossa and at the convexity. Lesions which are least likely to be detected by current CT techniques fall into two categories: (1) small lesions involving or adjacent to the hypothalamus, optic chiasm and optic nerve, and in the cerebellopontine angle and (2) primary vascular lesions, whether looking for the source of subarachnoid hemorrhage or occlusive disease (the CT scan may show the infarct but will give no specific information about the condition of the vessel).

The accuracy of this technique in its initial evaluation has been very promising. In the first 500 patients examined at the Mayo Clinic, the error rate was 3.6 percent (of the patients in this series who had other neuroradiological studies done, the corresponding error rates were pneumoencephalography, 2.1 percent; angiography, 6.5 percent, and isotope scans, 35 percent). There are certain lesions which have a characteristic pattern allowing a specific diagnosis. These include epidural and intracerebral hematoma; porencephalic, colloid and epidermoid cysts; cystic craniopharyngioma and cholesteatoma and pineoloma. The CT scan will be of particular value with trauma patients: intracerebral hematomas can be very easily differentiated from contusion, laceration and edema. There are other conditions in which the Mayo group found a high degree of diagnostic correlation (hydrencephalus, 92 percent; metastasis, 69 percent; dementia or degenerative states, 67 percent, suspected mass lesion, 62 percent, and infarction, 48 percent).

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Endoscopic Pancreaticholangiography (EPCG)

ENDOSCOPIC PANCREATICHOLANGIOGRAPHY (EPCG) provides valuable diagnostic information in patients with diseases of the pancreas and biliary tree. A side-viewing fiberoptic endoscope is visually directed into the duodenum and the papilla of Vater identified and cannulated with a flexible polyethylene tube. Injection of roentgenographic contrast material and fluoroscopic spot filming shows the anatomy of the pancreatic and biliary ducts.

EPCG is indicated in patients with (1) abdominal pain of unknown cause to corroborate a suspicion of pancreatic disease, (2) chronic relapsing pancreatitis for evaluation of possible surgical intervention, (3) suspected pancreatic carcinoma—patients with pancreatograms suspicious of carcinoma may undergo repeat cannulation for aspiration-cytology of pancreatic secretions, (4) obstructive jaundice—unlike transhepatic cholangiography, EPCG does not require immediate laparotomy and (5) postcholecystectomy syndromes.

Hazards of EPCG include those associated with any endoscopic procedure. In up to 45 percent of patients who undergo endoscopic pancreatography, there will be a transient elevation of serum amalyse without evidence of clinical pancreatitis. In approximately one percent of patients in this group, there will be clinically significant mild pancreatitis. EPCG is hazardous in patients with pancreatic pseudocyst because of the increased risk

of infection. These patients may be identified by ultrasound examination. EPCG is contraindicated in acute pancreatitis because an increase in pancreatic duct pressure during injection of contrast material may exacerbate the acute attack. Before jaundiced patients undergo EPCG, negative results of tests for hepatitis-associated antigen should be obtained to avoid the possibility of disseminating hepatitis virus. Patients with jaundice and a history of ascending cholangitis should receive antibiotic coverage before EPCG to avoid sepsis precipitated by retrograde injection beyond a biliary obstruction.

It is difficult to precisely evaluate the accuracy of EPCG at this time. It is certainly extremely accurate in the evaluation of the biliary tree provided that enough contrast material is injected to completely visualize the entire biliary tree. The accuracy of EPCG in pancreatic disease is less well known. Results of a recent study done by David S. Zimmon and associates state that in 34 of 63 patients (54 percent), the initial clinical diagnosis of pancreatitis was changed or more accurately defined, and in 21 of 63 (33 percent), an indication for surgical operation was established by the procedure. The number of patients with pancreatic disease in whom pancreatograms give completely negative findings is not presently known.

The most recent study of complications related to EPCG was done by Bilbao and co-workers. In the study, results of 10,435 EPCGs done by 402 operators in 220 centers across the United States were compiled using questionnaires. A 70 percent overall success rate with a 3 percent incidence of complications was shown. Although transient evaluation of serum amylase was commonly noted after EPCG, the incidence of clinically apparent pancreatitis was about 1 percent. This was usually mild, and was not associated with any fatalities in Bilbao's series. Death related to EPCG occurred in a small number of patients with biliary obstruction, pancreatic duct obstruction or pseudocysts.

In some centers, such patients—those at increased risk of infection—are put on antibiotics before the procedure. Time and well-controlled clinical studies will show whether this will decrease the incidence of fatal infectious complications of EPCG. Some routinely add chloramphenicol (Chloromycetin®) to the Renografin-60® (meglumine diatrizoate [52 percent] and sodium diatrizoate [8 percent]) used for duct injection. Both the success rate and complication rate are related to the experience of the operator. EPCG appears to be the procedure of choice in patients with obstructive jaundice. Patients with chronic relapsing pancreatitis, persistent abdominal pain associated with pancreatitis and complications of pancreatitis such as pseudocysts should have EPCG for accurate staging of their disease and planning possible surgical intervention.

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Drainage of Obstructed Kidneys by Percutaneous Nephrostomy

PERCUTANEOUS NEPHROSTOMY is a safe and effective method for relief of obstruction to a kidney. The technique is a modification of antegrade pyelography and makes use of skills and instrumentation from angiography. The obstructed kidney is localized either by ultrasound or by intravenous or retrograde administration of contrast material. Under fluoroscopy an 18 gauge Longdwell needle is inserted into a dilated upper calix, and the Teflon® sheath from the Longdwell needle is left in place in the collecting system. Through the sheath a guide wire is passed into the renal pelvis. The Teflon sheath is then removed and a multiple side hole angiographic catheter is inserted over the guide wire. Location of the catheter is checked radiographically and the catheter is sutured to the skin. Progressively larger catheters are used to obtain an eventual 18 F catheter size for permanent use. The catheter eventually should be soft rubber or sialastic to prevent damage to the kidney. The tube should have as many side holes as possible to allow free drainage. A closed system is constructed by connecting the catheter to a collection bag.

Minor complications have been encountered which for the most part are self-limited. These include (1) bleeding associated with initial needle puncture and guide wire manipulations, (2) perforation of a calix by the guide wire, (3) mucosal

edema from presumed catheter irritation and (4) calculus encrustation in the catheter.

A potential problem of this procedure might be erosion of the collecting system by a stiff catheter. It is therefore mandatory to check the position of the catheter to ensure that the tip is not abutting against a wall. Soft catheter material should be used as early as possible.

Infection within the perirenal space and catheter tract is also a potential hazard. We have not had this complication arise, although we have maintained patients on antibiotic coverage. However, in patients who initially had infected urine this complication has not developed.

Proposed contraindications would be the presence of renal neoplasm or renal tuberculosis. Hemorrhagic diathesis would also be considered a contraindication.

The technique is suitable for patients who are not surgical candidates for any reason. It may also be used as a temporizing treatment to buy time when other approaches are hazardous or before a more complex or definitive procedure can be carried out.

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Lactose-Barium Study as a Screening Test for Lactase Deficiency

INTESTINAL LACTASE DEFICIENCY is a condition in which there are low levels of lactase in the small bowel mucosa. This makes it difficult for lactose to be digested, a commonly occurring disaccharide.

Since the original description of the use of a lactose-barium mixture for the diagnosis of intestinal lactase deficiency, several studies have assessed its accuracy. Recently, Morrison and coworkers found that this radiographic procedure was 90 percent accurate in predicting lactase deficiency. Therefore, this simple test is an excellent screening procedure for discovering patients with low lactase levels. While many people with lactase deficiency are asymptomatic, there are also those with vague abdominal complaints who are unaware that their symptoms are related to lactose ingestion. By the routine use of a lactose-barium mixture, a radiologist may make the diagnosis of lactase deficiency which was unsuspected by both the patient and clinician. The radiographic features of the condition have been well described and consist of (1) rapid transit of the lactose-barium mixture through the small intestine, (2) dilatation of the small bowel and (3) dilution of the lactose-barium mixture in the small intestine.

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Lymphographic Patterns in Lymphoma

CERTAIN HISTOLOGICAL subtypes of lymphoma present a typical lymphographic appearance. Therefore, non-Hodgkin's lymphoma of the poorly or well-differentiated lymphocytic types—or of the mixed lymphocytic-histiocytic type (the old lymphosarcoma group)—characteristically present a homogeneous lymphographic picture. All or almost all of the visualized nodes are involved and show a similar pattern and degree of abnormality. Sharply defined intranodal filling defects are uncommon.

In contrast, Hodgkin's disease of the nodular sclerosis or of the mixed cellularity type shows a nonhomogeneous overall appearance on the lymphangiogram. Only some of the nodes are abnormal. The degree of nodal abnormality varies and well marginated filling defects are frequent. Lymph stasis is most often evident in this group.

Hodgkin's disease of the lymphocytic predominant type resembles the pattern of lymphosarcoma except that filling defects may occur. Non-Hodgkin's disease of the histiocytic type (reticulum cell sarcoma) is lymphographically similar to Hodgkin's disease of the nodular sclerosis type, but lymph stasis is less frequent.

In experienced hands, the lymphangiogram is more than 90 percent accurate in the diagnosis of lymphomatous involvement of visualized retro-

peritoneal lymph nodes. The majority of errors are of the false-positive type and are caused by benign reactive changes such as fibrosis, sinus histiocytosis and follicular hyperplasia, which distort the internal nodal architecture. Such changes are relatively common in patients with lymphoma. Therefore, although characteristic findings on the lymphangiogram do suggest a specific histiopathologic diagnosis, biopsy and other clinical investigations remain necessary for patient management.

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Methods for Acceleration of Small Intestinal Radiographic Examination

BECAUSE OF THE normal variation in transit time of barium through the small intestine, it often requires several hours for completion of this study. Numerous methods have been suggested for accelerating barium transit. These have included using a larger volume of barium, placing the patient in the right lateral decubitus position during the examination, using cold barium and giving pharmacologic agents including neostigmine or metoclopramide.

In a study in which three methods were compared with a control study in each of 20 volunteers, the addition of 10 ml of Gastrografin® (meglumine diatrizoate [66 percent] and sodium diatrizoate [10 percent]) to the barium mixture proved to be the best method for acceleration of small bowel transit of barium. The other methods used were the subcutaneous injection of 0.5 mg of neostigmine and placing the patient in the right lateral decubitus position during the examination. The average transit time in the control study was one hour (with a range of 15 minutes to three hours), while the average transit time using 10 ml of Gastrografin added to the barium was 33 minutes (with a range of 15 to 45 minutes). Therefore, the addition of 10 ml of Gastrografin to the barium provides a simple method for faster and more efficient radiographic examination of the small intestine.

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Bifid Ureter with Blind-ending Branch —the Radiologist's Role in Diagnosis

A BIFID URETER with one blind-ending branch is a rare congenital anomaly. These have the same histologic layers in their wall as the normal ureter and are not acquired ureteral diverticula.

There are two types of this anomaly which presumably represent abortive attempts at ureteral duplication from an accessory ureteral bud of the wolffian duct. They most commonly arise from the pelvic portion of the ureter and extend cephalad. The more common type is short and ends below the inlet of the pelvis. The second type is a longer blind portion which has a bulbous proximal dilatation. The latter usually has a small cap of nephrogenic tissue associated with it without any continuous connection. The nephrogenic tissue may be seen to "blush," especially when laminagraphs are obtained.

The distal segment usually joins with the accompanying ureter, although occasionally they may insert separately into the bladder or into an ectopic location.

The symptoms which are produced include flank pain, dysuria, fever and hematuria and are usually related to some complication involving the blind-ending segment. These complications range from reflux, infection, calculus formation within the blind portion and uroepithelial tumor. In addition, they may produce obstruction to the normal adjacent ureter and lead to secondary obstructive changes in the ipsilateral kidney.

The differential diagnosis of such a finding is an acquired diverticula which histologically lacks the full wall layers, a blind-ending stump post

heminephrectomy or a congenital blind-ending duplication of the ureter.

The diagnosis is more easily made by retrograde pyelography but may be suggested on excretory urography with reflux of contrast material up the blind-ending side when there is a normal appearing, nonduplicated upper collecting system.

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Ultrasound for the Study of Retroperitoneal Lesions

ULTRASOUND SCANNING has become important in the diagnosis of several diseases located in the retroperitoneum. It is a noninvasive test and often shows lesions which are not visible on ordinary x-ray studies.

Pancreatic tumors measuring 3 cm or more are regularly identified when located in the head and proximal body. Pseudocysts are also diagnosed with a high degree of accuracy. Acute pancreatitis is seen as an edematous organ, though associated bowel gas may prevent its visualization.

Retroperitoneal adenopathy greater than 2 cm is readily seen, especially when it presents in the periaortic chains. Pelvic node masses are often more difficult to demonstrate than upper abdominal disease.

Ultrasonic scanning has been particularly useful in the workup of renal masses discovered by intravenous urography. It accurately differentiates solid masses from those containing fluid, making it possible to determine which patients require angiography and which can be investigated more easily by percutaneous cyst puncture.

The abdominal aorta is readily shown and can be accurately measured in suspected aneurysms. The examination can also be repeated periodically to evaluate enlargement in a known aneurysm. This is especially useful when the aneurysm is not calcified and therefore not visible on an x-ray film of the abdomen. Since the aortic lumen and outer wall are both seen, a partially clotted aneurysm is sometimes measured more accurately by ultrasound than by aortography, which opacifies only the lumen.

The diagnostic accuracy of ultrasound in several diseases is currently in the range of 90 percent or better and recent improvements in commercially available equipment are now making even more diagnostic information available.

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The Single Nonfunctioning Thyroid Nodule: A New Approach to Diagnosis and Treatment

THE SOLITARY hypofunctioning thyroid nodule has long posed a diagnostic dilemma for the clinician and the surgeon. Nonfunctioning thyroid nodules are composed of a heterogeneous group of lesions which include both benign and malignant solid lesions as well as cystic lesions. Many studies have shown that approximately 20 percent of solitary hypofunctioning thyroid nodules are benign thyroid cysts.

The determination of whether a solitary cold thyroid nodule is cystic or solid cannot be reliably determined by x-ray studies, palpation or radioisotope scanning. Diagnostic ultrasound, however, now allows the differentiation between solid and cystic thyroid nodules to be made quite easily, provided the nodules are larger than 1.5 cm in diameter.

Our experience, as well as the results of other investigators, confirms the accuracy of ultrasound in identifying cystic thyroid nodules. Therefore we feel that the most rational approach to the workup of a solitary palpable thyroid nodule would first include a radioisotope scan, and, if the lesion is shown to be hypofunctioning, an ultrasonic examination should next be done. If the lesion is then shown to be cystic, the treat-

ment should be conservative, with primary needle aspiration and cytologic examination of the cyst fluid. This diagnostic workup will avoid the unnecessary expense and risk of thyroid operation. Should the ultrasound examination show that the nodule is solid, then the usual course of workup and therapy may be pursued. This may include a course of medical management to determine response to a drug regimen. In cases of no response to therapy, the patient may then be referred to surgery.

In all cases, however, the addition of diagnostic ultrasound to the workup will allow a significant number of patients to be spared the risks of general surgical procedures.

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EDITORIAL

Infectious Pericarditis

THE PERICARDIUM, an organ with limited and limiting functions, is a structure which man appears to be able to do without quite nicely, but which when injured can be the source of serious disease and life threatening pathophysiologic dysfunction. Like an actor with a limited repertoire, the pericardium when diseased can express its discomfiture in only several ways: by causing pain, by developing effusion or by fibrosing and constricting. The latter produces problems by restricting ventricular filling and interfering with the function of the enclosed heart or by a giant effusion compressing lung and interfering with pulmonary function.

From among all the diseases of the pericardium, in this issue of the JOURNAL, the Division of Infectious Diseases of the Harbor General Hospital focuses on the infectious causes of pericarditis in some detail. As usual, those problems which are still without definitive answers or which are still involved in controversy stimulate the most interest.

Idiopathic benign pericarditis remains the most common form of pericarditis in man. As is often the case with "idiopathic" disease, benign pericarditis is generally believed to be of viral cause.[1] Unfortunately, when the viral cause of idiopathic benign pericarditis is prospectively investigated, the virus continues to be elusive in most cases. For instance, Johnson and co-workers found evidence of a viral cause in five of 34 patients with acute benign pericarditis,[2] and Fowler in a prospective study of 25 cases of acute pericarditis found evidence of viral infection in only four.[1]

The inability to find the virus in these cases may be a manifestation of the limits in the techniques of viral identification and propagation that are presently available. Other explanations for our failure to grow virus from the patient's fluid or tissue, or to show active antibody response to viral antigen, are possible, however. It may be that viruses are only one of several causes of the clinical entity known as idiopathic benign pericarditis. Increasingly evident in experimental work is the fact that viral invasion can alter cells due to the continued presence of viral antigen or the development of antibodies to heart muscle such that persistent cellular dysfunction may occur long after the disappearance of viable virus. Such a mechanism may be responsible for the known tendency for idiopathic pericarditis as well as the other apparently noninfectious forms of pericarditis occurring after myocardial infarction and after pericardial injury and cardiac surgery to recur, often a number of times.[3]

Once the mechanism which results in recurrence is understood, we will be in a better position to prevent recrudescence and especially to treat the rare patient who has repeated episodes of disabling pericarditis and who presents an extremely difficult management problem. Occasionally in these patients it is necessary to employ analgesics, steroids, antimetabolite therapy[4] and finally pericardiectomy,[5] each associated with its own set of problems. The etiologic role of antiheart antibodies and autoimmune damage is as yet unclear in all forms of pericarditis. Engle and co-workers reported in a prospective, double-blind study, the close correlation of the presence of heart-reactive antibody in high titer in the serum of patients in whom the post-pericardiectomy syndrome developed after cardiac surgery.[6] The similarity of the clinical features of idiopathic pericarditis to those in the other forms of pericarditis—such as ones occurring after injury to the pericardium or after myocardial infarction—suggests a common underlying mechanism of injury. Such would be the case if each of the inciting injuries resulted in an autoimmune response which caused the clinical disease we recognize as pericarditis.

Tuberculous pericarditis remains a problem in diagnosis and management. The classical description of tuberculous pericarditis is that of a clinically insidious, chronic disease. It is less well

recognized that tuberculous pericarditis can initially manifest itself as typical acute pericarditis. The problem of the definitive identification of tuberculosis as the etiologic agent in pericarditis is of some importance since, unrecognized, the mortality approaches 80 to 90 percent with this disease.[7] Medical therapy alone appears to be less than totally satisfactory once the tuberculous nature of the pericarditis is recognized. Carson and associates reported that medical therapy in 62 consecutive patients with tuberculous pericarditis achieved satisfactory results in less than a third of the patients. Half of their patients required pericardiectomy for recurrent pericardial tamponade or constriction.[8]

With the increasingly smaller number of young people in this country for whom results are positive on tuberculin skin tests, purified protein derivative of tuberculin (PPD) has become more valuable in recognizing tuberculosis as a specific cause of pericarditis. A positive reaction on a skin test, however, simply tells us that the patient has had previous exposure to the tubercle bacillus, not that the pericarditis is caused by tuberculosis. At present, especially in young people with pericarditis, a positive reaction on a skin test is usually sufficient to start the patient on 12 to 18 months of antituberculous therapy. Even with the relative innocuousness of the drugs, though isoniazid and other antituberculous drugs are not without serious side effects, it would be preferable to establish the diagnosis positively before committing the patient to such a long and possibly difficult course of therapy.

Pericardiocentesis is helpful in definitely establishing the diagnosis but unfortunately at most only 50 percent of patients aspirated have positive cultures for tuberculosis.[9] If the usefulness of pleural biopsy in establishing the tuberculous cause in pleural effusion is analogous to pericarditis, the increased use of open pericardial biopsy should be considered more frequently, especially in younger patients in whom tuberculin skin tests give positive findings. If the biopsy specimen shows caseating granulomata or cultures Mycobacterium tuberculosis, the cause is established and the patient needs a full course of antituberculous therapy. If the biopsy specimen shows nonspecific pericarditis, the physician would be justified in withholding antituberculous therapy.

Because of the high incidence of constriction in tuberculous pericarditis, as mentioned, early diagnosis is most important. The role of steroids in preventing the development of constriction in tuberculous pericarditis is still unclear, and controlled studies to show the possible efficacy of this therapy are complicated by the relative rarity of the disease and therefore the difficulty in accumulating a large enough series in any one institution.

Once constrictive pericarditis is well established, the necessity for pericardiectomy is well recognized. Less well appreciated, especially by internists and cardiologists, are the problems confronting the surgeon who must find tissue planes and carry out an adequate pericardiectomy without injury to the coronary arteries and extensive damage to the underlying myocardium. Early identification of pericardial fluid organization or myocardial restriction would be beneficial in that early pericardiectomy could be done before extensive fibrosis involves the myocardium and obliterates cardiac surface structures. Early recognition of organizing pericardial fluid and early constriction could be recognized at the time of pericardial biopsy. The operative mortality from pericardiectomy, which at present can be as high as 29 percent,[10] would probably be reduced if the surgical procedure could be done early.

Of great interest is the changing nature of the infectious agents attacking the pericardium. To a large degree this changing flora is related to the improvement in our ability to treat infectious, malignant and immunologic diseases. With the introduction of antibiotics the incidence of pneumococcal percarditis, certainly among the commonest of organisms causing purulent pericarditis in the past, was notably reduced.[11] At present, with the manipulation of man's bacterial inhabitants by antibiotics and the interference of defense mechanisms by steroids and immunosuppressive agents, we are seeing the increasing incidence of infections, including purulent pericarditis, caused by saprophytes and previously nonpathogenic bacteria and fungi. A high index of suspicion allowing us to recognize purulent pericarditis is essential, for the penalty for overlooking the diagnosis is a mortality approaching 100 percent.[12]

Finally, although it is stated that constrictive pericarditis is unusual as a sequela of purulent pericarditis, it most certainly does occur and must not be overlooked. It has been especially noted in very young patients and can occur within a matter of weeks after the acute infection has been treated apparently adequately with antibiotics.[13] The frequent necessity for surgically draining the pericardium in purulent pericarditis must again be

emphasized and because of the possibility of constriction the patient must be followed carefully after the recognition of purulent pericarditis to detect the earliest signs of this complication.

It is obvious that there are still many areas both in the diagnosis and management of patients with pericardial disease where definitive answers are not presently available. It is interesting—and somewhat disappointing—that, as one looks back at the overview of pericardial disease written by Connolly and Burchell in 1961,[3] many of the same still unanswered questions are asked. As long as this is true, interest and research in the area of pericardial disease will continue to remain clinically important.

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Medical Accidents and Medical Accident Insurance

PERHAPS IT IS TIME to get back to the old idea that doctors are really trying to do their best in taking care of their patients and to recognize that, since doctors are human like other people, they may make mistakes even while they are trying to do their best. The mistakes may be in judgment or in something they do or do not do. In times past this was an accepted assumption and often there was little recourse for the patient who was the unfortunate victim of a doctor's mistake. This was wrong and there has been a great change since tort law became applied both extensively and effectively in the medical field. The extent of this redress adjudged by the courts in favor of patients has now become very great. It is becoming abundantly clear that the physician, the hospital or the insurance company can no longer pay the cost of these judgments and the expensive litigation that attends them, and there is beginning to be some question as to whether these costs should be passed on to the patient population or whether they should be spread over an even wider base.

But let us return to the idea that the doctor tries to do his best. Certainly there is no reason to believe that doctors want to do their worst or that they seek to damage or injure their patients. It seems that any such instance would or should be a criminal offense. Given that the intent is good, the limited numbers of mistakes and unfortunate outcomes which inevitably occur are more in the nature of accidents—unexpected events which occur and which none of the parties involved plan or expect to happen. If these incidents, tragic though they may be, are viewed as accidents much as injuries or diseases sustained while working for an employer are viewed, then the situation seems to clarify. It can then be admitted that medical accidents can and do happen and that no one need be particularly at fault even though errors in judgment or action may have been made. It can also be admitted that the patient or medical-accident victim is entitled to some acceptable compensation for his unlucky or unfortunate outcome. The costs could then be kept within the capability of the health care industry, which includes physicians, to pay. And fully as important, practicing physicians and hospitals could return to giving their whole attention to trying to do their best for the patient instead of

diverting ever-increasing effort and attention to trying to protect themselves in case of possible litigation at some future time.

The vast majority of malpractice or professional liability incidents are really accidents. Nobody planned them or expected them to happen. There are many who believe that an entirely new approach and an entirely new solution to the medical malpractice problem has become necessary. Is it not time to recognize medical accidents for what they are, to use the term "medical accident," to talk about "medical accident insurance" and to find a new solution within this frame of reference? It would seem so.

—MSMW

Laetriles — Not a Vitamin and Not a Treatment

ONE OF THE CRUELEST manifestations of man's inhumanity to man is the preying by cancer quacks on patients who have, or believe they have, cancer. The loss of life consequent to delay in effective treatment and the anguish and pain resulting from mismanagement of patients by cancer quacks are incalculable, while money wasted in payments to cancer quacks in the state of California conservatively is estimated at 20 million dollars each year.[1]

Laetrile (amygdalin, beta-cyanogenetic glycosides, nitrilosides, vitamin B_{17}) is the unproven anticancer agent now most widely used in California as well as in the United States generally. The widespread therapeutic administration of this material to cancer patients continues in spite of the fact that, as Dr. David Greenberg documents in this issue of the JOURNAL, the rationale offered for its use—the selective release of lethal amounts of hydrocyanic acid in tumor cells—is spurious and based on erroneous premises. As these facts have become apparent the proponents of Laetrile have modified their claims, now calling the material vitamin B_{17} and advocating its use as an "antineoplastic vitamin" for the prevention of cancer. As Dr. Greenberg points out these hypotheses and claims also are spurious.

Clinical evidence that laetriles are *not* effective in the treatment of cancer repeatedly has been presented during the past 22 years by (among others) the Cancer Commission of the California Medical Association,[2] the California Cancer Advisory Council,[3,4] the National Cancer Institute,[5] the United States Food and Drug Administration[6] and the American Cancer Society.[7] The California State Board of Health has prohibited the use of Laetrile in California,[8] and the United States Food and Drug Administration has banned shipment of the material in interstate commerce.[9]

Because of interest in Laetrile, responsible agencies and investigators have conducted very extensive studies of its potential antitumor effect in many animal systems, and are prepared to conduct scientifically controlled clinical evaluation of the material if scientifically valid evidence exists justifying such trials. To date no such evidence has been presented or discovered. In 1973 an unpublished preliminary study was quoted by the promoters of Laetrile as suggesting that the material inhibited the growth and metastasis of mammary carcinoma in mice.[10] Subsequent studies in the same institution have not confirmed the unreported initial study.[11] Extensive testing of Laetrile in many animal models recently has been supported by the National Cancer Institute, which has indicated that the material does not possess antitumor activity in any of the experimental systems.[12]

With such a preponderance of evidence indicating the worthlessness of Laetrile for the treatment of cancer, why do patients still seek and accept such therapy? Why is it still used? What can or should be done about it? The answer to these questions necessitates a consideration of the promoters of Laetrile, the patients who accept this therapy and the physicians who should be responsible for the medical management of cancer patients.

The promoters of Laetrile reap huge financial returns, a fact which primarily is responsible for continuance of its availability. They are unable or unwilling to accept the rules of evidence and the scientific and ethical approach to evaluating the effectiveness of Laetrile. They assume the role of underdog and claim prejudicial, unfair and discriminatory treatment by the orthodox medical community. It is exremely unlikely that the attitudes and actions of these proponents can be modified by any rational approach or scientific evidence documenting the ineffectiveness of Lae-

trile. The illegality of the promotion and use of Laetrile has not to date prevented an increase in its use. Enforcement of the California law has been and is being pursued by the State Department of Health, but has not prevented an increase in the use of Laetrile. It is improbable that the anticancer quackery law and its enforcement will eradicate the use of Laetrile, although these steps decrease its availability. Additional approaches are necessary.

The patient who seeks and accepts treatment with Laetrile does so largely because of fear of death and disability from cancer, and because of disillusionment or distrust of orthodox physicians and treatment. Frequently such patients engage in "magical thinking" and accept as valid the claims of quacks that Laetrile is a miracle drug which will cure when other treatment will not. Also, many of these patients have a strong tendency to support the "underdog" (the quack) and his claims and to reject the "establishment" (orthodox physicians and therapy). Many patients sense a feeling of frustration and hopelessness conveyed, perhaps unconsciously, by the physician who tells them the nature and probable outcome of their disease—a natural feeling on the part of the physician who is discouraged by his recognition that he cannot cure the patient. Patients sensing this hopelessness frequently are unwilling to "abandon hope" and therefore seek the false reassurances of the fraudulent claims of the cancer quack.

It is improbable that a rational presentation to the frightened patient of the fraudulent nature of cancer quackery will modify his human emotional behavior. After all, scientific evidence of the worthlessness of Laetrile has been available for a quarter of a century and has not been particularly effective in decreasing patient acceptance of the material. Probably all that can be done to diminish patient reliance on quackery is to improve the relationship between patient and physician, and convince patients that they must trust their physicians to do all that humanly is possible to control the disease.

Perhaps the most promising approach to diminishing the influence of the cancer quack is to improve the capacity of the physician to cure and manage neoplastic disease, and to modify the physician's attitude toward cancer and the cancer patient.

Management of neoplastic disease with radiation and chemotherapy has improved tremendously during the past twenty years. Previously fatal or rapidly progressive diseases now may be "cured" (for example, acute lymphocytic leukemia in children and certain types of Hodgkin's disease) or comfortable life remarkably prolonged despite disease (in cases, for example, of acute leukemia in adults, and carcinoma of the prostate and breast). If the physician rendering primary care to the cancer patient is not prepared to provide the most effective treatment for cancerous disease, such treatment now is readily available in most communities from qualified hematologists or oncologists who are prepared to provide the best in modern cancer therapy.

Equally important in the management of a cancer patient is the attitude of the physician providing treatment. He must convey to the patient his belief that cancer is a treatable and potentially curable disease, and that modern cancer therapy has great benefits for the cancer patient—far greater than can be offered by a cancer quack or a nostrum such as Laetrile. If the physician does not abandon hope neither will his patient, nor will the patient abandon proper medical management to seek spurious magical remedies.

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Early Prevention of Atherosclerosis

ARTERIOSCLEROTIC CARDIOVASCULAR DISEASE remains the leading cause of death in the United States and in most of the other industrialized nations of the world. Extensive prospective epidemiologic studies have identified a number of characteristics of the coronary-prone subject. Among those factors associated with the greatest increments of risk are hyperlipidemia, hypertension and smoking, all of which potentially may be modified. In fact, the residual risk associated with a family history of coronary disease is small when the risk increments attributable to these factors are removed. These findings have stimulated a number of intervention studies, using dietary modification or drugs, in which the majority of subjects, however, have been in or beyond the fifth decade of life. Nevertheless, moderate decreases in the incidence of new coronary events or of death from coronary heart disease have accompanied dietary modifications which result in significant reduction of serum cholesterol levels.[1,2] The results of drug treatment of patients with previous myocardial infarctions have varied from moderate decreases in mortality for certain patient subgroups[3,4] to little discernible effect.[5] The finding that atherosclerotic changes are often present in the coronary arteries even in patients in their early twenties[6,7] indicates that measures directed at primary prevention in the general population will have to be begun during adolescence, and probably earlier for persons with primary hyperlipoproteinemias. The statement of position by the California Society of Pediatric Cardiology and the California Heart Association which appears in this issue of the JOURNAL endorses this view.

Recent progress in the investigation of mechanisms of atherogenesis lends support to the belief that the three principal risk factors enumerated above reflect important elements in the process of plaque formation. That blood platelets interact with injured arterial endothelium, resulting in hyperplasia of smooth muscle elements in the arterial wall, is now appreciated.[8] Modification of platelet behavior by hyperlipidemia[9] may amplify this platelet-dependent process as well as thrombogenesis. Accumulation of lipids from lipoproteins containing apolipoprotein B, which has a demonstrable affinity for certain connective tissue elements,[10] appears to account for the initial appearance of lipid in the lesion. Thus, elevated levels of either beta (low density) or prebeta (very low density) lipoproteins in serum would be expected to accelerate this process. Hypertension leads to vascular injury. Smoking exerts effects on plasma free fatty acids and upon platelet behavior in addition to its hemodynamic effects. The association of elevated levels of beta and prebeta lipoproteins (but not of high density lipoproteins), with accelerated appearance of coronary vascular disease is amply confirmed by available epidemiologic data.

The question of whether early prospective modification of these factors will significantly reduce the ultimate risk of coronary vascular disease cannot yet be given a definitive answer for our population. However, the intimate relationship of risk factors identified in epidemiologic studies with essential elements in the process of atherogenesis, along with the remarkably lower incidence of coronary disease in populations in which plasma lipid levels are much lower, suggests that such modification is likely to be efficacious. Clearly, treatment of hypertension and abstention from smoking result in demonstrably reduced morbidity and mortality. Attempts to modify serum lipoprotein levels by changes in diet, even in childhood, appear indicated as well, since surveys of children and adolescents in the United States show serum cholesterol levels much higher than those found in age-matched populations in countries with lower incidences of coronary disease.[11,12]

Beyond caloric restriction, the simplest dietary modification is restriction of the daily intake of cholesterol to approximately 300 mg. This would be expected to result in a reduction of 10 to 15 percent in serum cholesterol levels. A further decrement of similar magnitude can be obtained by sharp restriction of saturated fat, an objective much harder to achieve because of prevailing American dietary habits. However, profound modification of diet probably should not be undertaken in infancy—or even in the first four or five years of life—until more is understood about the nutrition of the very young.

While the measures outlined above are prob-

ably sufficient for the general population, primary hyperlipidemia presents a special situation even in childhood. Since the primary forms of hypertriglyceridemia generally tend to appear in the early adult years, the predominant form of genetic hyperlipidemia in childhood is hyperbetalipoproteinemia. Many persons with this pattern of hyperlipoproteinemia are now known to carry one or more dominant genes for defective binding of beta lipoprotein to cell membranes.[13] Persons with elevated levels of beta lipoprotein can be identified by measurement of serum cholesterol level alone, obviating the requirement for fasting. Since most persons with this disorder are asymptomatic in childhood and since its prevalence probably exceeds one-tenth percent in our population, measurement of serum cholesterol levels is reasonable in multiphasic screening of children. Clearly, all children should be studied in kindreds in which early coronary vascular disease, hyperlipidemia or xanthomatosis occur.

The response of many persons with primary hyperbetalipoproteinemia to modifications in diet is disappointing. Since this disorder results in demonstrable acceleration of coronary atherogenesis,[14] combined diet and drug treatment in childhood may be indicated. Drug treatment of children heterozygous for hyperbetalipoproteinemia should still be regarded as experimental, with emphasis on the identification of effective agents. However, the fulminant atherogenesis encountered in homozygotes requires energetic treatment with the most effective regimen now available. This appears to be a combination of bile acid-binding resin and nicotinic acid.[15]

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PSRO Update—1975

IT IS NOW more than two years since PL 92-603 with its mandate for Professional Standards Review Organizations (PSROs) became the law of the land. The two hundred and three PSRO areas were established on schedule. Much of the overt opposition has subsided but quite considerable disquiet and uncertainty remain. And they will remain until there is some indication of whether the overall effect of PSRO implementation will improve patient care or impair it—and if it does improve it, whether the cost in time and dollars to operate the inevitably cumbersome machinery will prove to be worth the benefit. It is safe to say that many practicing physicians remain skeptical and unconvinced.

The establishment of local PSROs is in progress but it is proceeding more slowly than called for by the law. It appears that by January 1, 1976 (the date when the Secretary of Health, Education, and Welfare becomes empowered to establish PSROs in areas which do not yet have them), only about one half or two thirds of the designated areas will have local PSRO organizations which will qualify for conditional or planning status under the law. This slowness is at least in part due to inadequate federal funding for the program.

There are a number of other problems in the planning for PSROs which so far have not been re-

solved. Some of these seem to relate to conflicting aims inherent in the program itself. One pertains to the need to collect adequate medical practice data for PSRO review and yet preserve confidentiality for both patient and physician. While the need to do both these things has been acknowledged, the mechanism for their accomplishment has so far not been determined. A second issue yet to be resolved is what the relationship is to be between cost control and quality assurance in the program. This may well be settled by the outcome of the present struggle for bureaucratic control of the program between "H" and "W" within the Department of Health, Education, and Welfare. The Social Security Administration (SSA) in "W" pays the bills and has a primary interest in controlling costs, while the Bureau of Quality Assurance in "H" is responsible for "standards" and is more concerned with assuring the quality of medical care for the American people under federally-mandated programs. It is not yet clear which, or whether either, will gain control. Perhaps some kind of modus vivendi will be worked out at the interface between them. Perhaps utilization review and quality assurance will evolve as separate and unrelated programs. There is much at stake in all of this, not only for the bureaucracies concerned, but for the American people as well.

A third issue which in time will require resolution is the relationship of national standards to locally developed standards for medical care in the PSRO program. At the moment an attempt to develop national standards is under way while local PSROs are being given to understand that they will be responsible to develop and enforce local standards for quality assurance and utilization review in their own designated area. Whether national or local standards will prevail remains to be seen. It is also worth noting that so far relatively little attention is being paid to the relationship of these "standards" to the case of any particular patient who may really not need all the treatment the standards specify or who may need some additional or different treatments. What will the incentives be for a physician to treat his patient according to the book or according to what he believes will serve the patient best?

But perhaps the most portentous aspect of PSRO 1975 is the underfunding of the program which is now becoming evident. Not only will this impede or prevent a substantial number of physician-sponsored PSROs from qualifying under the law by January 1, 1976, but even more importantly it will deter or at least delay the development of the nationwide capability for local PSRO responsibility. Already this is preventing the advancement of many PSROs from planning to conditional status. It is also worth noting that a relative shortage of funds in federal programs results in a tendency to keep the funds and therefore the programs centralized, whereas generous or even adequate funding encourages the decentralization of both responsibility and dollars. It is quite possible that moderate underfunding of the PSRO program will pervert its purposes by fostering centralization at the expense of developing the local responsibility and control which was the original intent. Severe underfunding could obviously destroy the program entirely—with physicians, no doubt, then erroneously being held to blame.

There are many human endeavors that require a balance to be struck between opposing or conflicting forces if there is to be any sort of satisfactory outcome. It appears that the PSRO program may be such an endeavor. It may well be that its success or failure will depend upon how successfully a balance can be struck between the conflicting forces just described, and on whether or not the government's commitment to the program is sufficient to provide adequate funding for it. Perhaps a "PSRO Update—1976" will have the answers.

—MSMW

CASE REPORTS

Refer to: Kahn O, Cohen KL, Wilkins HE: Cardiomegaly—A possible factor in permanent endocardial pacing. West J Med 122:331-334, Apr 1975

Cardiomegaly

A Possible Factor in Permanent Endocardial Pacing

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PERMANENT ENDOCARDIAL PACING is a proven and highly satisfying mode of therapy for controlling selected cardiac dysrhythmias. Since its inception, a decade ago,[1] prosthetic endocardial pacing has increased in usage as safer and more sophisticated units have been developed.[2,3] Several factors still of major concern to physicians employing this tool, however, are the safety, efficiency and effectiveness of treatment. The present morbidity for this form of treatment ranges from 28 percent to 63 percent.[4,5] The immediate mortality, however, varies from 0 to 6.7 percent,[4,5] with a long-term mortality (five years) of 15.1 percent.[4] This compares very favorably to a medically treated group which had a four year mortality rate of 80 percent.[6] Although permanent pacing is quite effective, the high morbidity rate still leaves much to be desired. This report deals with heart size at the time of pacemaker implantation as a factor that significantly influences morbidity. Two case histories are presented to emphasize the complications relative to heart size at the time of permanent pacemaker implantation.

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Reports of Cases

CASE 1. *Cardiomegaly with decrease in heart size, consequent perforation and acute loss of ventricular capture.* A 57-year-old woman with diabetes controlled by diet, presented with acute anterior myocardial infarction complicated by complete heart block and congestive failure. A temporary bipolar electrode and external demand mode prosthetic cardiac pacer was used to effect a viable rhythm. The patient had a prolonged stormy hospital course in an intensive care unit, complicated by low cardiac output syndrome, congestive heart failure, systemic hypoxemia, pneumonitis and pneumothorax. The patient slowly improved with intensive medical treatment, but after four weeks continued to be dependent on a prosthetic cardiac pacer.

Since a large anterior myocardial infarction had occurred with present cardiac compensation but continued dependence on a temporary cardiac pacemaker (and even though cardiomegaly persisted), it was decided to implant a permanent endocardial demand mode (ventricular inhibited) pacemaker (Medtronic model No. 5942 with No. 5818 electrode). This was accomplished without difficulty. During the following five days, the heart size decreased remarkably from a cardiothoracic ratio of 67 percent (Figure 1A) to 55 percent (Figure 1B). The "loose-loop" (Figure 1A) of the right atrial portion of the pacing electrode became retroverted (Figure 1B, arrow) and tightly impacted against the lateral right atrial wall. On the evening before discharge, the electrode tip perforated acutely (Figure 1C) with consequent loss of ventricular capture and intercostal muscle stimulation. This necessitated retraction of the pacing electrode some 3.5 cm to again attain a position of ventricular capture (Figure 1D). Recovery was uneventful with early discharge and no consequent complications (such as hemopericardium or infection).

CASE 2. *Mild compensated cardiomegaly with further stress-induced cardiomegaly (congestive heart failure after operation) and transient exit block.* An 86-year-old man with diabetes controlled by diet and an oral antihyperglycemic

agent, and with symptomatic complete heart block and mild cardiac decompensation, was admitted to the hospital and successfully treated with diuretics. However, sinus rhythm did not return. Consequently, a permanent endocardial demand mode (ventricular inhibited) pacemaker (Medtronic model No. 5942 with No. 6901 electrode) was implanted (Figure 2 Left). A 0.5 milliampere ventricular capture threshold was obtained with good ventricular endocardial sensing potentials. The patient's postoperative course was interrupted by acute peritonitis secondary to a ruptured colonic diverticulum, necessitating a defunctioning colostomy. Although a stormy hospital course ensued, the patient finally recovered.

After 13 months, the patient was admitted to hospital for an elective transurethral prostatectomy. Postoperatively, congestive heart failure developed with more cardiomegaly (Figure 2 Right) and a transient period of minor exit block (rare ventricular noncapture) which responded to antifailure treatment (administration of digitalis, di-

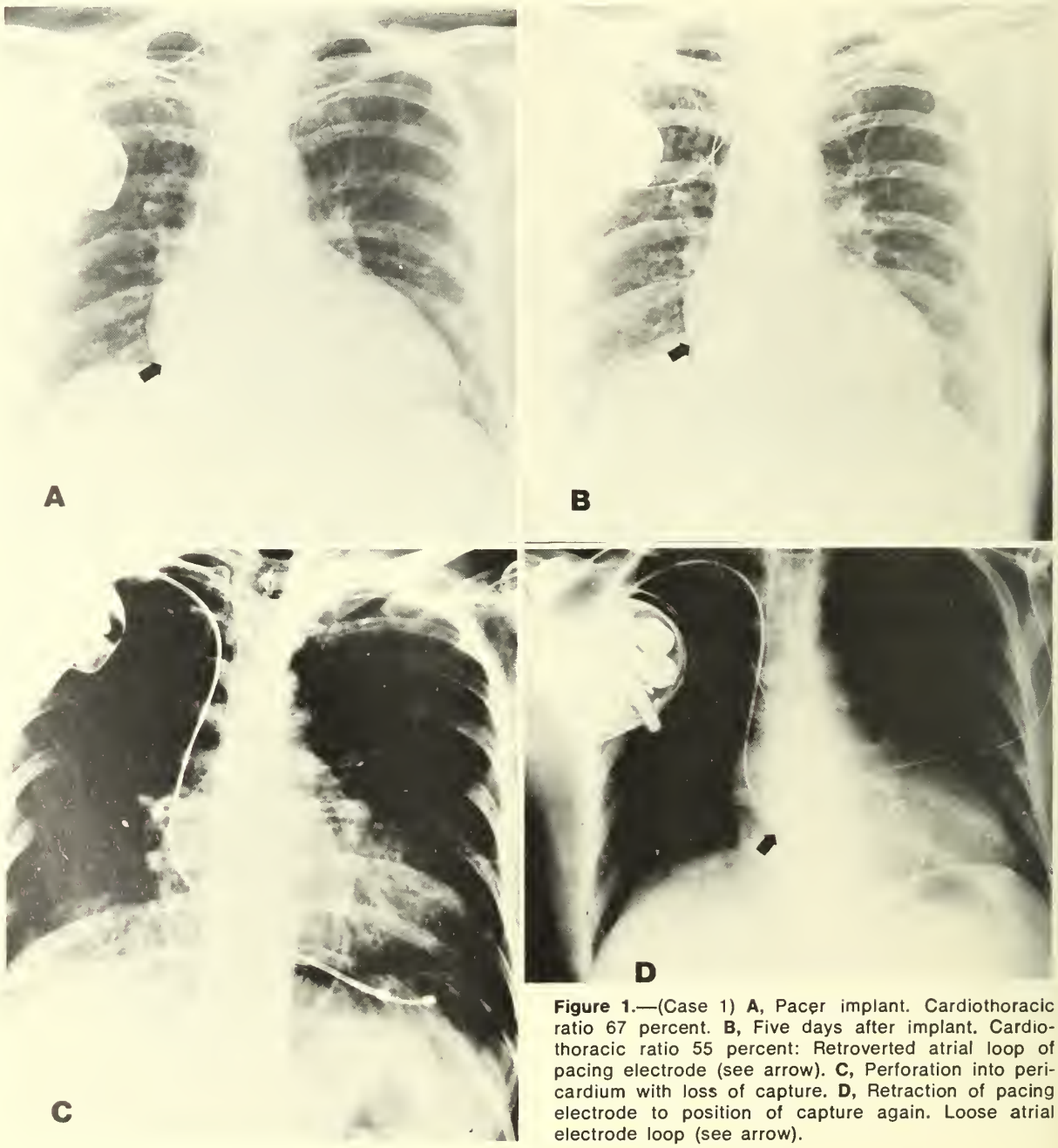

Figure 1.—(Case 1) **A,** Pacer implant. Cardiothoracic ratio 67 percent. **B,** Five days after implant. Cardiothoracic ratio 55 percent: Retroverted atrial loop of pacing electrode (see arrow). **C,** Perforation into pericardium with loss of capture. **D,** Retraction of pacing electrode to position of capture again. Loose atrial electrode loop (see arrow).

uretics, and sodium restriction) within 48 hours. Full prosthetic pacemaker capture ensued after a decrease in cardiomegaly. The demand mode pulse generator was prophylactically replaced 30 months later. Ventricular capture thresholds were measured at that time and found to be 1.7 milliamperes. The patient was discharged and continues at the present time to enjoy good health.

Discussion

These cases are presented to draw attention to changes in heart size as one of the causes of acute or chronic loss of ventricular capture to prosthetic endocardial pacing, an often frustrating problem to physicians concerned with this mode of therapy. The cases are remarkably similar in some respects (for instance, loss of ventricular capture) but the similar features have different underlying causes.

In the first case the heart size decreased with electrode perforation and loss of capture; in the second, it increased with consequent transient exit block and loss of capture even in a chronically implanted electrode. The first case of severe cardiomegaly was treated aggressively with temporary prosthetic cardiac pacing and diuresis for four weeks with minimal response. It was, therefore, decided that the cardiomegaly was static. A permanent cardiac pacer was implanted for the bradydysrhythmia, wedging the endocardial electrode in the apex of the right ventricle as well as insuring a loose, smooth, gentle, free curve of the endocardial electrode in the right atrium.[7] Subsequently, the apparent static cardiomegaly decreased significantly in the immediate postimplant period to cause electrode perforation and acute loss of ventricular capture. This was effectively treated with no sequelae. A decrease in cardiomegaly in the postimplant period is, however, relatively common, occurring in approximately 50 percent of cases.[8] A definitive explanation for this frequent phenomenon is presently still lacking.

In the second case (mild compensated chronic cardiomegaly) it was 13 months postimplantation when further cardiomegaly suddenly developed, secondary to cardiac decompensation associated with surgical operation. There was consequent minor electrode displacement (negative x-ray evidence) and transient exit-block with minor loss of ventricular capture. After medical treatment and cardiac recompensation with minor decreasing cardiomegaly by x-ray, the exit block resolved with good ventricular capture once again. At the time of elective pulse generator replacement some 17 months later a low (1.7 milliampere) ventricular capture threshold was measured.

These two cases raise many questions regarding endocardial pacing, a better and probably a safer method than epicardial pacing.[9] However, in epicardial pacing, cardiac size is not a crucial factor to electrode-myocardial contact and consequent ventricular capture. Some of the questions raised by these two cases include:

- What is optimal static heart size?
- Is heart size in disease ever static?
- When is the optimal time of electrode implantation after myocardial infarction?
- How should the electrode be wedged in the right ventricular apex?

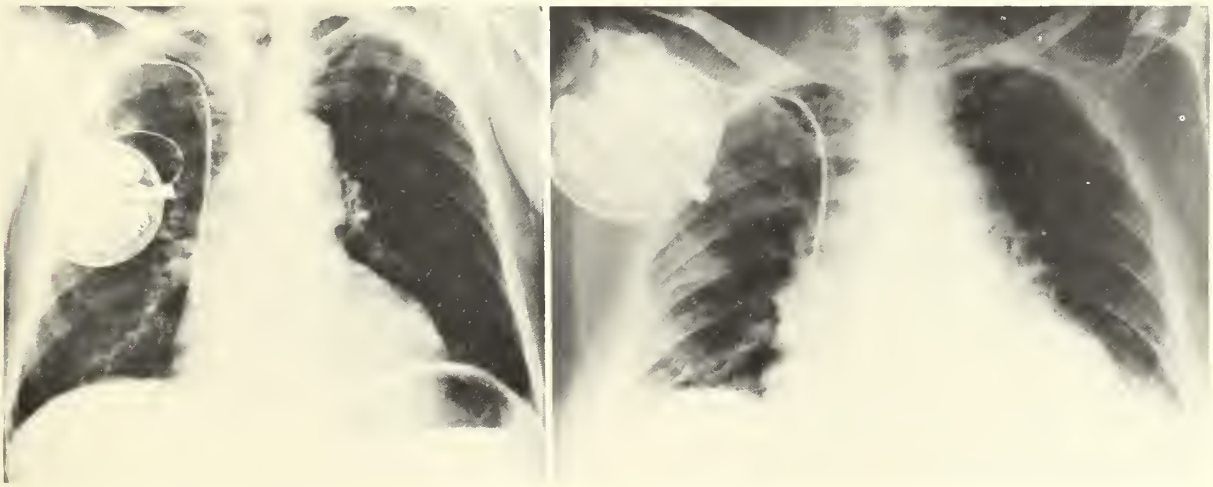

Figure 2.—(Case 2) **Left,** Decompensated cardiomegaly with transient exit block. **Right,** Compensated cardiomegaly with capture again.

• When, if ever, is the electrode firmly fixed and seated in the right ventricular apex?

• How much redundant "electrode loop" should be allowed in the right atrium?

Needless to say, the questions raised by these cases cannot be dogmatically answered. The answers, as with many aspects of medical practice, depend on the subjective judgment and past experience of each individual physician. Objective ground rules can be applied in a general way but cannot be guaranteed to strictly apply in an individual case. The rules only serve as guidelines; perhaps to decrease risk factors. Nevertheless the relatively high morbidity rate (63 percent)[5] suggests the need for a more stable and tenacious endocardial pacing electrode. Endocardial pacing electrodes have vastly improved over the past decade[10] but there is still a great need for improvement. The ideal electrode would seem to be one that would not displace or perforate on change in heart size, would seat and fix firmly within 24 hours of implantation and would lend itself to easy removal at anytime in the event of possible problems—for instance, fracture or infection. Unfortunately, such an electrode is not as yet available.

Summary

We have presented two cases of endocardial pacing that were associated with loss of appropriate ventricular capture and function because of changes in heart size that were not anticipated before insertion of the electrode system. One was due to decreasing chronic cardiomegaly with consequent perforation and the other was due to increasing cardiomegaly with exit block. We believe dynamic heart size to be a significant factor in the morbidity associated with this mode of therapy.

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Refer to: Kretschmer KP, LaZerte GD, Pass BR: Polypoid lesion of cecum. West J Med 122:334-337, Apr 1975

Polypoid Lesion of Cecum

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NEOPLASMS OF THE COLON commonly are found to be the cause of intestinal obstruction or bleeding. Most of these tumors turn out to be either adenomatous polyps or carcinomas. A few of them prove to be mesenchymal tumors such as lipomas, leiomyomas or lymphomas. Only rarely does the mass prove to be an inflammatory lesion or "pseudotumor." Reported cases of non-neoplastic masses in the gastrointestinal tract have occurred chiefly in the stomach, small bowel and rectum. Most of them have been the result of unexplained lymphoid overgrowth and usually have been termed lymphoid polyps or pseudolymphoma.[1] This report describes a different kind of polypoid pseudotumor presenting in the cecum, associated with chronic inflammation and ulceration of the appendix, and resulting in gross hemorrhage per rectum.

Report of a Case

The patient, a 25-year-old black woman, was admitted to the hospital with a two-day history of bloody stools and frank rectal hemorrhage without any associated gastrointestinal symptoms. Five years before the patient had had an episode of rectal bleeding similar to the current one. On admission to another hospital, the presence of a sickle cell trait was noted. The hemocrit was 31 and serum iron was 39 mg per 100 ml. Results of upper and lower gastrointestinal series and

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Figure 1.—Polypoid lesion of cecum shown by barium enema.

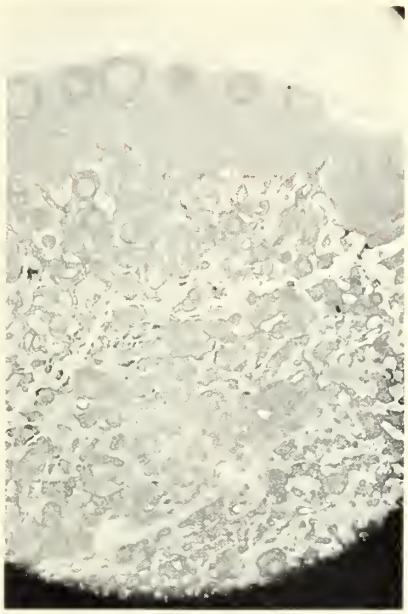

Figure 2.—Section of hyperplastic lymph node, using hematoxylin-eosin stain (reduced from 20×).

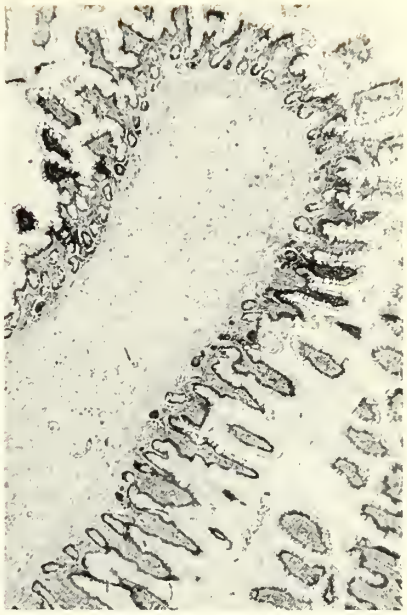

Figure 3.—Section of ileum, using hematoxylin-eosin stain, showing edema (reduced from 50×).

sigmoidoscopy were all reported to be normal. The cecum, however, was not well shown in any of the films. The bleeding stopped spontaneously and the patient was discharged with the diagnosis of gastrointestinal bleeding of undetermined origin.

The patient remained well until gross bleeding began again a few days before the present admission. Findings on physical examination were unremarkable. Initial hematocrit was 37, dropping to 31 on the second hospital day. Results of upper gastrointestinal series, small bowel follow through and sigmoidoscopy were normal. A barium enema study showed a polypoid mass along the medial aspect of the cecum (Figure 1). Findings on surgical exploration of the abdomen were normal with the exception of the ileocecal area. A firm mass was palpable within the cecum, the surrounding fatty tissue was indurated and the overlying serosa was puckered and thickened. The appendix could not be identified. Large nodes were palpated in the mesentery of the right colon and terminal ileum. En bloc resection of the right colon, including the mesentery to the origin of the ileocolic artery and ileocolostomy, was carried out. The patient had an uneventful postoperative course and was discharged one week later. There has been an absence of symptoms ever since (32 months as of January, 1975).

Gross dissection of the excised specimen showed the last 10 cm of the ileum, the cecum and 15 cm of the ascending colon all matted together in fatty tissue traversed by fibrous bands. The lymph nodes were found to be enlarged up to 2 cm and discrete on cross section, with a prominent follicular pattern (Figure 2). The mucosa of the ileum was intact and edematous (Figure 3). The mass within the cecum was a group of multilobulated polyps (Figure 4), some of them arising from the ileocecal valve and all covered by smooth and intact mucosa of normal thickness. The individual polyps ranged from a few mm up to 2 cm in size and some of them were fused together at the tip, their slender stalks forming arches and bridges across the lumen of the gut. The appendix could not be identified externally but examination from the lumen of the cecum showed a stubby diverticulum about 2 cm in length and 1 cm in diameter in the expected position of the appendix. The lining of this small diverticulum appeared red and granular and was continuous with small (1 by 0.1 cm) linear ulcerations in the mucosa of the cecum. Sections through the red granular area showed that the mucosa was extensively ulcerated with pronounced lymphocytic and plasmacytic infiltration extending through the muscular wall. Scant purulent exudate was present on the luminal surface with underlying hyperplasia of capillaries forming granulation tissue which occasionally projected above the surface. A trichrome stain con-

Figure 4.—Opened specimen, with ileum on the right and ascending colon above and out of focus. The ileocecal valve is distorted by multiple polyps on the cecal side. The arrow points to an opening thought to be the appendiceal remnant.

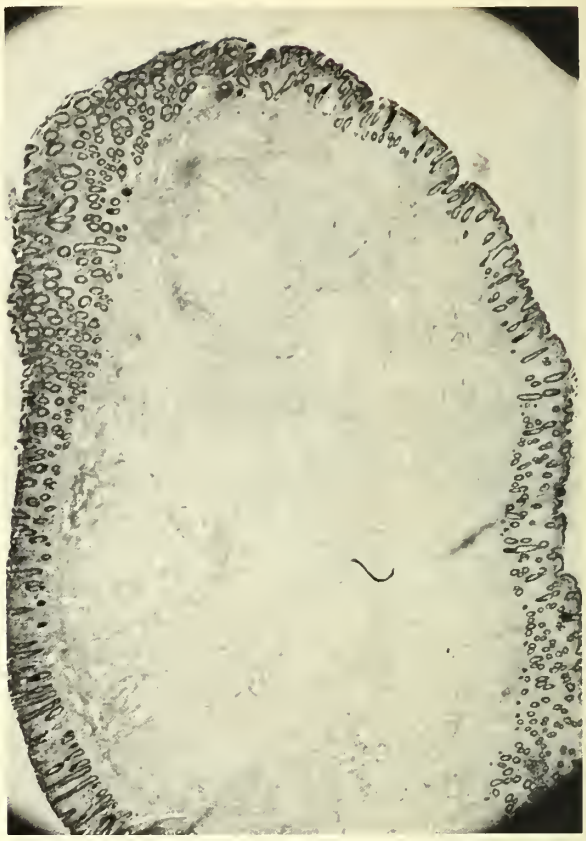

Figure 5.—Section of typical polyps, using hematoxylin-eosin stain (reduced from 20×).

firmed the presence of two layers of muscle in the wall of the diverticulum, proving that it was the appendix and not a sinus tract. The polypoid structures were formed of a great proliferation in submucosal connective tissue sprinkled with a variety of inflammatory cells and covered by well-ordered mucosa with hyperplasia of mucosal lymphoid tissue (Figure 5).

Discussion

Painless rectal bleeding presents a difficult differential diagnostic problem, particularly in younger patients. Rectal examination, sigmoidoscopy and barium enema often fail to provide a clue, and even at exploration it may be impossible to identify the bleeding source. Recently, arteriography has become a valuable diagnostic tool, provided that the bleeding is brisk. Diverticular disease and carcinoma are the two most common causes of rectal bleeding, but are unusual in the young. Inflammatory bowel disease of granulomatous or ulcerative origin rarely presents without associated gastrointestinal symptoms. Familial polyposis of the colon, Meckel's diverticulum, hemangiomas and Wilkies ulcers are less common causes which have to be considered in the differential diagnosis.

In the case reported here, a barium enema study showed a localized polypoid mass in the cecum. The smooth contour and the suggested translucency of the filling defect led us to the preoperative diagnosis of lipomatous hyperplasia of the ileocecal valve, a benign condition that may present as silent gastrointestinal hemorrhage.[2] At exploration the gross appearance of a firm ill-defined mass involving the whole thickness of the bowel with serosal puckering, retraction of the mesentery and large regional nodes suggested the possibility of lymphoma or infiltrating carcinoid tumor—both of which have a predilection for the ileocecal region. Consequently, en bloc resection was done. On pathologic examination the findings were those of chronic inflammation with polyp formation. The submucosal connective tissue proliferation, lymphangiectasia and transmural spread to the mesentery suggested granulomatous enteritis but despite exhaustive search we were unable to show the presence of any granulomata. Per-

sistent ulceration with active inflammation was found mainly in the mucosa of the remnant of the appendix which was centrally embedded in the inflammatory mass. Localization of the disease to this one segment of the bowel and the absence of granulomata led us to discard the possibility of granulomatous enteritis in favor of the more optimistic diagnosis of chronic nonspecific infection arising in the appendix.

Although the polypoid lesions are grossly similar, the pathologic changes in our case are quite different from those of the lymphoid polyps and pseudolymphomas described by Weaver and Batsakis.[1] A variety of inflammatory pseudotumors in the upper respiratory tract, stomach, small bowel and rectum have been described, but the case discussed here is the first to our knowledge to present as polyps in the cecum—probably as a result of persistent appendicitis.

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LETTERS *to the Editor*

Tumor Associated Antigens

To the Editor: In their review, "Tumor Associated Antigens—Clinical Implications," West J Med 122:91-92, Jan 1975, Franco and his colleagues mention that HCG, CEA, and AFP are used to monitor patients with malignant disease but they do not discuss the similar application of calcitonin measurement.

The measurement of calcitonin by radioimmunoassay is a well-documented procedure for the diagnosis and management of patients with medullary thyroid carcinoma.[1] This tumor is a neoplasm of the calcitonin-secreting parafollicular (C) cells of the thyroid, and, therefore, produces abnormally elevated plasma concentrations of calcitonin.[2,3] Basal and stimulated concentrations of calcitonin as measured by radioimmunoassay differentiate patients with medullary thyroid carcinoma[1,3] from normals. Measurement of calcitonin can establish the diagnosis of this tumor very early in the course of the disease.[4] This is of special importance in screening the relatives of patients affected with this tumor which can occur in a familial pattern.[5] Localization of tumor by selective venous catherization has also been shown.[1,6] Most recently, reports of ectopic calcitonin production suggest that hormone measurements may be useful in monitoring the course of selected patients with tumors other than medullary thyroid carcinoma.[7] Therefore, calcitonin should be added to the list of tumor associated antigens which can be used for the diagnosis and management of patients with cancer.

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More on Breast Cancer

To the Editor: I would like to comment on the paper on "Diagnosis of Carcinoma and Benign Cysts of the Breast" by Dr. Walter deGroot, West J Med 122:99-103, February, 1975

The comments concerning the indications and usefulness of aspiration of cysts are pertinent. It is worth emphasizing that the presence of carcinoma in a cyst wall is exceedingly rare and that, therefore, cyst fluids will rarely yield positive cytologic results. On the other hand, a correctly negative cytologic report does by no means exclude the possibility of the presence of carcinoma in adjacent breast tissue. I have seen carcinoma cells only once in over 1,000 breast fluid specimens but consider it likely that carcinoma was present in several of the breasts that were examined. I do not believe that the decision whether the aspirated fluid is to be examined cytologically should be made on the basis of the fluid being clear or cloudy. Most cyst fluids are cloudy, bluish, or brown. This cannot be correlated with a greater likelihood of malignancy. As a matter of fact, in the exceptionally rare case of a cystic carcinoma the fluid might be relatively clear.

Aspiration smears of masses suspected to be carcinoma should not replace an excisional or incisional biopsy. However, if a cytopathologist who is experienced in the interpretation of these specimens is available, an immediate positive cytologic diagnosis particularly in advanced disease or patients with large tumors may at times be advantageous and save operating room time. Traditional biopsy and frozen section examination should of course remain the standard diagnostic procedure. The paper stresses that needle core biopsies are preferable to aspiration smears and are more reliable. Because of the small size of these specimens and frequent distortion, the evaluation of these biopsies is often quite difficult and is probably no more reliable than the interpretation of good aspiration smears by an experienced pathologist.

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Trauma Rounds

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This is one of a series of Conferences on Trauma at San Francisco General Hospital

Refer to: Lewis FR: Current concepts in cardiovascular monitoring (Trauma Rounds). West J Med 122:339-344, Apr 1975

Current Concepts in Cardiovascular Monitoring

CAROL RAVIOLA, MD:* The patient we would like to discuss today is a 63-year-old woman who was admitted 12 hours ago, having been injured when her runaway automobile crushed her against the door of her garage. She was admitted within thirty minutes of injury and was in shock with poor peripheral skin perfusion, and a blood pressure of 80/60 mm of mercury. The injuries appeared to be limited to the lower abdomen and pelvis. Her abdomen was diffusely tender and the pelvis was grossly unstable.

Findings on x-ray studies included a fracture of the right iliac crest and superior and inferior pubic rami and a right sacroilic separation. On laparotomy, one hour after admission, a large retroperitoneal hematoma was noted, which filled the pelvis and extended upward on the right nearly to the diaphragm. This was not entered. After thorough exploration of the abdominal cavity showed no additional injuries, the abdomen was closed. The patient received 5 units of blood during the induction of anesthesia and the surgical procedure.

Immediately after operation, peripheral perfusion was poor. The patient's toes appeared blue and mottled, the blood pressure was 140/90 mm of mercury and the pulse rate was 100 beats per minute. Central venous pressure was 10 cm of water. One unit of blood was given over the first two hours after operation and the central venous pressure rose to 25 cm of water. Urine output which was 30 ml the first hour, fell to 20 ml the second hour. A Swan-Ganz catheter was threaded into the pulmonary artery after 1½ hours of manipulation. The wedge pressure was 7 to 8 cm of water and additional volume was given with an increase in urine output and stability of vital signs.

The patient's condition is still critical at this time and we would like to ask Dr. Lewis if he would discuss the indications for pulmonary artery catheterization and discuss its use in monitoring the critically injured patient.

FRANK LEWIS, MD:† In patients admitted with serious injuries, the problem of monitoring can be divided into cardiovascular and respiratory components. Today, as requested by Dr. Raviola, I will limit my discussion to the newer sophisticated cardiovascular monitoring techniques used in the Intensive Care Unit at San Francisco General Hospital.

Two questions arise when patients are in clinical shock. One is, what is the patient's volume status relative to the capacity of the vascular tree? A second is, how well is the heart pumping the load of fluid which is being delivered to it? All of the forms of shock can be defined in terms of alterations in volume status or cardiac action: for

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example, hemorrhagic shock is due to the lack of adequate circulating volume with a relatively normal intravascular capacity. Septic shock results from an expanded intravascular capacity with a blood volume that is inadequate to fill it. Cardiogenic shock results from ineffective pumping action even though the vascular capacity and volume are matched.

The problem of assessment of cardiovascular function can be divided into two different periods. The first consists of the initial assessment of cardiovascular function in the emergency rooms and during surgical procedures, and the second consists of the assessment of complicated problems such as the patient today presented in the postoperative period.

The initial period of assessment and resuscitation of the critically injured patient has been covered in a previous "Trauma Rounds" and I will confine my remarks to the venous pressure and more sophisticated measurements.

In the initial evaluation in the emergency room, the status of the neck veins will give a gross indication of venous pressure. This is often all that is needed in making immediate decisions about management (for example, a patient who is hypotensive because he "bled out" will have flat neck veins while the one who is hypotensive from a cardiac problem such as tamponade will have bulging veins).

Quantitative assessment of venous pressure is obtained using central venous pressure (CVP). A central venous pressure line is inserted in the emergency room through an antecubital vein. A long percutaneously placed commercial catheter can be used or, if veins are difficult to find, a cutdown on an antecubital vein can be carried out. A catheter is threaded upward into the great veins of the chest. If a cutdown is done, a long large-bore catheter such as a pediatric feeding tube should be used. This will permit rapid transfusion as well as the measurement of central venous pressure.

Once the CVP line has been placed, it is connected to a three way stopcock and a saline manometer. Readings should be made with the patient absolutely supine, and with the zero reference point chosen at the anterior axillary line. In order to prevent error from one observer to the other, it is convenient to mark the zero reference level on the patient so that discrepancies in readings do not arise from variations in selecting the base line zero. The errors in CVP readings result from three major sources: (1) the patient's position is not flat, (2) the zero reference point is not maintained the same from one reading to the next and (3) the position of the tip of the catheter is incorrectly located—either being outside the chest or else too far central and in the right ventricle. The former of these two difficulties can be avoided by watching the manometer level and noting the presence of good respiratory fluctuations. The second one can be avoided by noting the presence of ventricular pulsations when the CVP is being measured or by noting the location of the catheter tip on an x-ray film of the chest. A pressure below 3 to 5 cm of water is taken generally to indicate hypovolemia and the normal range is considered to be approximately 5 to 10 cm of water. Above the range of 12 to 15 cm of water, the pressure is clearly elevated. With tamponade, pressures of 30 to 40 cm of water are seen.

The central venous pressure has been used since the early 1960's as an indicator of volume status. It replaced nuclear medicine techniques for blood volume assessment which were relatively cumbersome and inaccurate. It has come under considerable criticism in recent years as to its accuracy. In many conditions, studies have shown that left atrial pressure or left ventricular end diastolic pressure do not always move in parallel with the central venous pressure. Particularly in instances where there is myocardial dysfunction (for example, mycardial infarction), the filling pressures on the two sides of the heart may differ. Individual reports have emphasized the variance which exists in many conditions—including sepsis, pneumonia and cirrhosis—but the main problem arises when there is myocardial or cardiac valvular disease or severe respiratory failure such as "shock lung."

In a study that compared central venous pressure (CVP) and left atrial pressure (LAP) in a group of normal people, there was a strong correlation between these two values. This is true in a patient with trauma in most instances as well. The central venous pressure is a valuable measurement, and its value should be not overlooked in the discussions which have gone on about subtle differences between the CVP and LAP. It is not as precise as the left atrial pressure in determining volume status, but in the average patient, and when it is carefully done, it is entirely adequate as a volume indicator in most clinical situations.

In the emergency room and in the operating room it has not yet proved practical or necessary

TABLE 1.—*Comparison of Swan-Ganz Catheters Showing Their Cost, Uses and Features.*

Type of Lumen	*Sizes*	*Cost*	*Uses and Features*
2	5,7F	$18	Pulmonary artery and wedge pressures. Aspiration of mixed venous blood
3	7F	35	Same as above plus side hole in right atrium for central venous pressure measurement
4	7F	65	All of features of three-lumen type plus thermodilution cardiac outputs

to consider more sophisticated monitoring. The central venous pressure therefore is the mainstay of volume monitoring in these two situations.

Once the patient is out of the operating room and in the intensive care unit, it may become necessary to have a more precise measurement of volume status in order to have better "fine tuning" of his fluid replacement. To obtain this, measurement of left atrial pressure is necessary. The most feasible means of obtaining this is to use the pulmonary capillary wedge pressure. In the last few years, the Swan-Ganz catheter has become available from Edwards Laboratories. It allows measurement of pulmonary artery and wedge pressures without the need to use x-ray or fluoroscopic control. Instead, the Swan-Ganz catheter can be placed while the patient is in the intensive care unit, using only a pressure monitor to determine the position of the tip.

A PHYSICIAN: *Would you describe the catheter?*

DR. LEWIS: The Swan-Ganz catheter comes in two sizes, 5F and 7F. The small catheter has a diameter of 1.6 mm and the larger, 2 mm. They may be introduced either through a cutdown or through a large bore needle. The catheters come with two, three or four lumens depending upon monitoring requirements. Table 1 gives a comparison of the various types of catheters, their cost and the features available in each.

The basic two lumen type is available in two sizes, and may be passed to the wedge position in the pulmonary artery so that pulmonary artery pressures and pulmonary wedge pressures can be measured with the end hole depending whether or not the balloon is inflated. In addition, mixed venous blood can be aspirated from the tip of the catheter to determine arteriovenous (AV) oxygen content differences. The three lumen catheter has essentially the same features but in addition a side hole is added approximately 20 cm proximal to the tip, which places it in the right atrium when the catheter is in the wedge position. This allows simultaneous measurement of the CVP, as well as the pulmonary artery pressure. The four lumen version incorporates the same features as the three but in addition has a small temperature sensing device (thermistor) at the tip of the catheter. With the use of this device the cardiac output can be determined by the thermodilution method. This technique requires the injection of cold glucose solution through the right atrial side port and then measuring the temperature change between the site of injection and the thermistor at the catheter tip. A time temperature curve so obtained can be easily analyzed to give direct reading of cardiac output. When the cardiac output as well as the arteriovenous oxygen difference is known, the patient's oxygen consumption can be ascertained.

DONALD TRUNKEY, MD:* *Could you describe the procedure for inserting a pulmonary artery line?*

DR. LEWIS: The method of insertion of a Swan-Ganz catheter is the following. Through a cutdown or introducer the catheter is advanced into the superior vena cava. Markings on the catheter at 10 cm intervals from the tip facilitate the placement. When the site of insertion is an antecubital vein, passage to the 35 cm mark will place the catheter in the superior vena cava. The balloon should then be inflated with the required amount of air, which in the case of the 5F catheter is 0.8 ml and in the 7F catheter is 1.2 ml. The catheter should also be connected to a strain gauge so that pressure at the tip can be continuously monitored. With the balloon inflated, the catheter is advanced while watching the pressure tracing. As the catheter tip reaches the right atrium, the flow of blood tends to drag the inflated balloon through the atrium and the tricuspid valve into the right ventricle. These locations can be assessed by noting the irregular phasic tracing with respiratory fluctuations when the catheter is in the vena cava, the accentuated and very regular atrial waves when the catheter enters the heart and then the high spiking ventricular pressure waves when the catheter passes through the tricuspid valve. Further advancement results in the catheter balloon being carried out the ventricular outflow

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track into the pulmonary artery where the high spiking systolic waves are accompanied by a measurable diastolic pressure.

From the main pulmonary artery the catheter tip is advanced into progressively smaller branches of the artery until it reaches a wedge position. At this point the catheter position is adjusted so that wedge readings reflecting the left atrial pressure can be taken with the balloon inflated while pulmonary artery pressures can be obtained with the balloon deflated. The normal procedure is to advance the catheter with the balloon expanded to the wedge position, deflate the balloon and look for pulmonary artery waves. The catheter is pulled back if necessary until the waves are seen on the monitor. The balloon is then reinflated to determine if a wedge pressure reading results. If not, the catheter is advanced slightly and the process repeated. Ultimately a position can usually be found where the wedge and pulmonary artery pressures are both obtainable. Should this not be possible, the catheter should be left in the free pulmonary artery position and not in the wedge position, since it will occlude the vessel when wedged and may produce thrombosis in the pulmonary artery distal to the catheter.

It is sometimes difficult to tell when the catheter passes from the right ventricle into the pulmonary artery, because the systolic pressure is the same in both and the upsweep of the pressure wave form is the same. However, the down slope of the pressure wave in the ventricle falls rapidly to the range of the central venous pressure. In contrast the downslope in the pulmonary artery is slower and there is usually a valve closing artifact visible along the downslope. In addition, the pressure does not fall to central venous levels but rather to pulmonary artery diastolic levels which is usually higher than the central venous pressure.

A Physician: *Is it possible to place the catheter in all patients?*

Dr. Lewis: Our success in passing the catheter has been similar to that reported in the literature. We have approximately a 95 percent success rate in passing the catheter into the pulmonary artery and can pass it into the wedge position in about three quarters of patients. In approximately 20 percent of patients, there will be premature ventricular contractions. The primary problem is the time required to pass the catheter and place it properly in the pulmonary artery. With experience this can often be accomplished in five to ten minutes but there are often times when it may take 30 minutes to an hour to place the catheter.

In general it is easier to place the 5F catheter because it is smaller and more flexible and seems to negotiate the curve in the ventricle more easily than the 7F. In certain instances failure to pass the 5F has been followed by success with the 7F and there is no definite way of predicting which will drop in most easily. We usually use the two lumen Swan-Ganz catheter. This allows the drawing of mixed venous blood as well as the sampling of pulmonary artery pressures, the most essential data that we require. In certain circumstances it may also be desirable to obtain cardiac output and in this situation the four lumen Swan-Ganz with the thermistor at the tip is used.

Once the catheter is in place, wedge pressure measurements can be obtained as often as needed to monitor the patient's volume status. This reading is a direct reflection of the filling pressure of the left atrium, therefore is the most accurate single number we have for determining the patient's relative volume status and myocardial function. The same pressure ranges as noted for the CVP also apply to the wedge except that they average 2 to 3 cm of water higher. Once the catheter is in place it can be left in for several days and is managed the same as any other indwelling venous line. In order to keep the lumen free of thrombus, a continuous slow infusion of heparinized saline or dextrose solution should be maintained.

The other advantage of using a Swan-Ganz catheter is that it allows mixed venous blood to be obtained. A cautionary note is in order, in that this blood must be withdrawn slowly with the

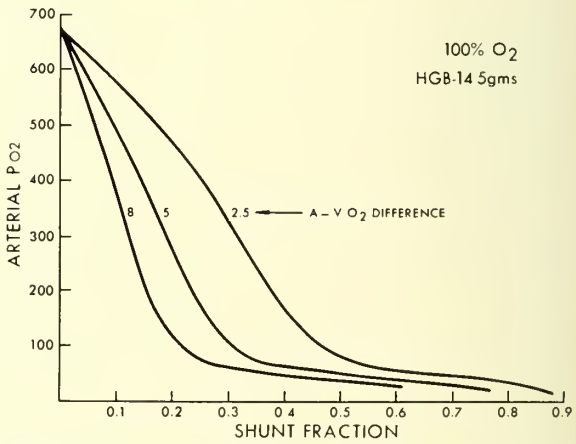

Chart 1.—Relationship between arterial oxygen pressure (pO_2) shunt fraction and cardiac outputs.

balloon deflated in order to prevent arterialized blood from being pulled back across the pulmonary capillaries, making the mixed venous sample appear more oxygenated than it actually is. The mixed venous blood allows two physiologic measurements to be obtained; the arteriovenous oxygen content difference and the pulmonary shunt fraction.

By measuring the oxygen saturation in arterial and mixed venous blood simultaneously, the content difference may be easily established. In a normal person the difference is 5 ml of oxygen per 100 ml blood. When the heart is pumping ineffectively, the fractional oxygen extraction from arterial blood increases and the mixed venous blood has a lower oxygen content than normal. Therefore, the AV content widens and when this exceeds 8 ml of oxygen per 100 ml of blood, cardiac function can be assumed to be inadequate. Therapy in these circumstances is directed toward the use of cardiotonic drugs if wedge pressure is high, or volume replacement if it is low. Similarly, the circulation may be hyperdynamic—as might be true in compensated septic shock or when defective red cell function such as that which follows massive transfusion is present. In this circumstance, the fractional oxygen extraction from arterial blood is lost, and the mixed venous blood returns with a higher oxygen saturation. In this situation the AV difference narrows. The normal content difference as noted is 5 ml of oxygen per 100 ml of blood but in the hyperdynamic patient it may narrow to 2 to 3 ml of oxygen per 100 ml of blood.

A simultaneous arterial blood gas assessment also allows determination of the fraction of blood shunted through the lungs without being oxygenated. This shunt calculation is the single best indicator of pulmonary decompensation in patients in whom "shock lung" develops. It parallels the arterial oxygen tension but is a better guide than that number because it is independent of cardiac output. The details of the calculation are readily available.[1] Suffice it to say that this calculation uses the mixed venous saturation, the arterial oxygen saturation and a knowledge of the inspired oxygen concentration which the patient is breathing. In a normal person, the shunt fraction is no more than 3 to 5 percent. In a patient with significant respiratory dysfunction from the adult respiratory distress syndrome, it may be 40 to 50 percent. The consequence of this is severe hypoxemia with which clinicians are familiar.

In Chart 1, the relationship between the arterial oxygen pressure (pO_2) and the shunt fraction is indicated with a patient breathing 100 percent oxygen. The purpose of the figure is to show the pronounced difference that occurs in arterial oxygen tension with differences in cardiac output, as reflected in the arteriovenous oxygen difference. The central curve is a normal situation while the curve on the right is the hyperdynamic state and that on the left is the situation with a failing circulation. In Chart 2, a vertical line has been drawn to represent a patient with a 20 percent shunt, a moderate degree of pulmonary dysfunction. The points at which it intersects each of the three curves indicates what the arterial pO_2 would be in each of those patients. The horizontal lines which are projected out to the X-axis indi-

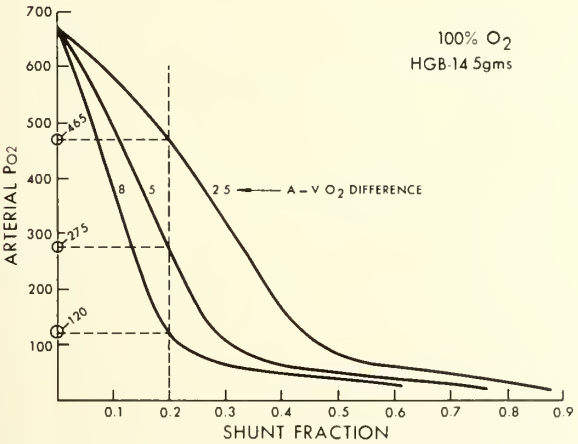

Chart 2.—Different arterial oxygen pressure (pO_2) values obtained at three levels of cardiac function in a patient with a 20 percent shunt fraction.

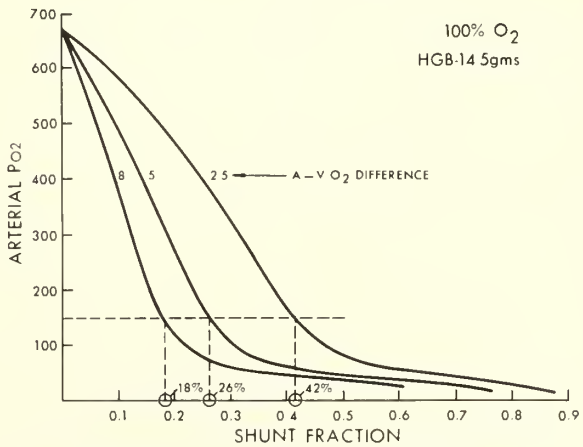

Chart 3.—The relationship between a fixed arterial oxygen pressure (pO_2) and cardiac function on the shunt fraction.

cate the values. It can be seen that in a patient in whom there is a failing circulation, the arterial pO_2 would be only 120 while in a normal patient it is approximately 275, and in a patient with hyperdynamic circulation it would be 465. In all three instances the shunt fraction, and therefore the relative degree of pulmonary impairment, would be the same. However, the arterial pO_2 could obviously be improved significantly by improving the cardiac output. In a patient with failing circulation, this would be a clear indication to give cardiac inotropic agents in order to improve oxygenation and allow the inspired oxygen concentration to be reduced.

In Chart 3, another use for the shunt determination is evident. A horizontal line has been drawn to represent an arterial pO_2 of 150. The points at which this intersects the three lines indicates the relative shunt in each of three situations mentioned previously and shows how the actual shunt fraction varies depending on the AV difference in a given patient. A patient with hyperdynamic circulation who had a pO_2 of 150 might actually have a shunt of 42 percent, and therefore severe pulmonary dysfunction, whereas a patient with failing circulation who had a pO_2 of 150 would have only an 18 percent shunt, a moderate degree of impairment. The arterial pO_2 alone, therefore, is an inadequate indicator of a patient's pulmonary status because it depends, to a considerable extent, on the state of the circulation. In an average patient the arterial pO_2 serves well and a detailed analysis of the pulmonary and cardiac systems is not needed. However, in a severely traumatized patient or one in whom there is a combination of cardiac and respiratory failure, or who appears to be in refractory shock with poor perfusion, it becomes essential to dissect out the relative contributions of the cardiac and pulmonary lesions. In this situation the Swan-Ganz catheter is a valuable adjunct and permits the precise titration of therapy.

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Refer to: Greenberg DM: Vitamin fraud in cancer quackery (Special Article). West J Med 122:345-348, Apr 1975

Special Article

The Vitamin Fraud in Cancer Quackery

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THE ATTEMPTED EXPLOITATION of the cyanogenic glucosides, particularly amygdalin—under the name Laetrile—in the treatment of cancer has a long history.

Amygdalin was first isolated from bitter almonds by the French chemists Robiquet and Boutron-Charlard in 1830. Liebig and Wohler observed that amygdalin was hydrolyzed with the evolution of benzaldehyde and hydrogen cyanide by an enzyme preparation from bitter almonds later named emulsin.[1] Later work showed that emulsin was an enzyme mixture containing among others, the specific enzymes beta-D-glucosidase and beta-oxynitrilase. Beta-D-glucosidase specifically hydrolyzes the beta-D-glucoside linkage. Liberation of benzaldehyde and cyanide from the released mandelonitrile is catalyzed by beta-oxynitrilase.

The two common laetriles are amygdalin and prunasin (Figure 1). Prunasin contains one less glucose molecule in beta-D-glucoside linkage.

When these compounds are cleaved by the enzyme beta-glucosidase there are liberated the sugar, glucose, and the cyanohydrin of benzaldehyde (mandelonitrile). As shown in Figure 2, the mandelonitrile decomposes to a slight degree spontaneously to benzaldehyde and hydrocyanic acid (HCN).

Laetrile has been promoted as an anticancer agent for many years. The Krebses (E. T. Krebs, Sr. and E. T. Krebs, Jr.) isolated a partially purified preparation from aqueous extracts of defatted ground seeds (U.S. Patent 2,464,240 [1949]). In recent years pure amygdalin, isolated from apricot kernels, is being used, legally in many foreign countries and certain of the states of the United States, and illegally in California.

In 1953, the Cancer Commission of the California Medical Association investigated the claims made for the use of Laetrile in cancer treatment and condemned its use. In 1959 the California Legislature passed Senate Bill 194, to provide a means for combating medical quackery in the diagnosis and treatment of cancer. On authority of this statute the use of Laetrile was made illegal. However, illegal treatment has continued and in recent years the traffic in Laetrile has grown enormously.

Purported Rationale for Laetrile Effect

As noted, the catalytic cleavage of amygdalin or prunasin by the enzyme beta-glucosidase liberates mandelonitrile, which decomposes spontaneously into benzaldehyde and cyanide. The cyanide is presumed to kill cancer cells, but not normal tissue, because in the latter there is postulated to be present large amounts of the enzyme thiosulphate transferase (rhodanese) which converts the cyanide to the less toxic thiocyanate. Cancer tissue is presumed to be rich in beta-glucosidase.[2a]

There are several flaws in this hypothesis:

- The available information shows the presence of only traces of beta-glucosidase in animal tissues and even less in amount in experimental tumors than in such organs as liver and kidney.[2b]
- The beta-glucosidase values reported for tumor tissue give a false picture, since the substrate commonly employed to test for this enzyme was *p*-nitrophenyl-β-D-glucoside. This compound has been observed in the laboratory of Dr. E. Conn at the University of California, Davis, to be an order of magnitude more active as a substrate

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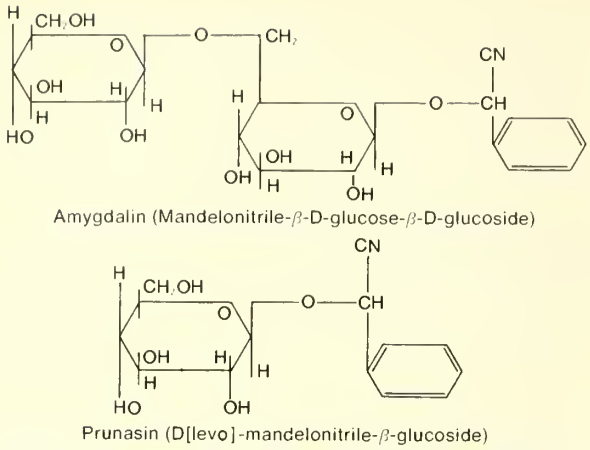

Figure 1.—Chemical structures of the two common laetriles, amygdalin (top) and prunasin (bottom).

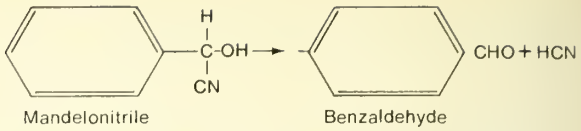

Figure 2.—Mandelonitrile, liberated when amygdalin or prunasin is cleaved by the enzyme beta-glucosidase, which decomposes spontaneously into benzaldehyde and hydrocyanic acid.

than amygdalin or prunasin when all are subjected to the action of glucosidase from liver.

- There is no evidence that there is any pronounced differential between the rhodanese content of comparable normal and cancerous tissue.[2b,2c]

There has been much shifting of ground by E. T. Krebs, Jr. to bolster the claim for Laetrile. One of these efforts was the claim that upon ingestion, amygdalin was hydrolyzed to mandelonitrile and the latter was transported intact to the liver where it was converted to the beta-glucuronide through the action of beta-glucuronidase. The mandelonitrile-beta-glucuronide was then supposed to be carried to cancer tissue and there again hydrolyzed by beta-glucuronidase to mandelonitrile.[3] This absurd proposition was stimulated by the publications of Fishman and Anlyan[4,5] that cancer tissue was rich in beta-glucuronidase.

In an earlier period it was assumed that laetriles were hydrolyzed by the enzyme beta-glucuronidase. This of course is erroneous; instead laetriles are specific substrates for beta-glucosidase because of their beta-D-glucoside bonding.

The Vitamin Theory—Alleged Vitamin B_{17}

In 1970 by a "brilliant" stroke, E. T. Krebs, Jr.[6] transformed the cyanogenic glycosides into a vitamin—a so-called antineoplastic vitamin B_{17}. In the following we will demonstrate the falseness of the claim that the cyanogenic glycosides have any properties akin to the known vitamins.

At a time when there is a considerable revolt against processed foods, and many individuals are receptive to almost any claim of the virtues of "natural" nutrition, the vitamin B_{17} claim has had a tremendous impact. Marketing of ground apricot kernels has sprung up and apparently is flourishing. Consequently, the claim for the anticancer properties of Laetrile has taken on added acceptance in some circles.

The claim of E. T. Krebs, Jr. that beta-cyanogenetic glucosides (lactriles), or *nitrilosides* as he terms them, are vitamins—specifically designated as vitamin B_{17}—and that a deficiency of this alleged vitamin is the cause of cancer is examined below and shown to be only a figment of his imagination.

What is a Vitamin?

A vitamin may be defined on the basis of several properties:

- It is a nutritional component of organic composition required in small amounts for the complete health and well-being of the organism.
- Vitamins are not utilized primarily to supply energy or as a source of structural tissue components of the body.
- A vitamin functions to promote a physiological process or processes vital to the continued existence of the organism.
- A vitamin can not be synthesized by the cells or the organism and must be supplied de novo.
- In man and in other mammals, deficiency of a specific vitamin is the cause of certain rather well-defined diseases. These include scurvy, beri beri, pellagra, pernicious anemia and rickets. These diseases are prevented or cured by addition of the appropriate vitamin.

Vitamins that are essential dietary ingredients for certain animal species may not be such for other animal species. One example of this is vitamin C (ascorbic acid) which is essential for man and for guinea pigs but not for most other mammals. The reason for this is that man and the guinea pig have lost the enzymatic machinery required for the synthesis of vitamin C, while this still persists in most other mammals.

Herbivores do not require the ingestion of vitamins in their feed, because of vast numbers of

bacteria present in their rumen. These bacteria can synthesize vitamins that may be lacking in the feed.

The claim that the beta-cyanogenic glycosides represent a new, hitherto unrecognized water soluble vitamin (vitamin B_{17}) is refuted by the following facts.

- No evidence has ever been adduced that laetriles are essential nutritional components.
- Laetriles have never been shown to promote any physiological process vital to the continued existence of any living organism.
- No specific disease has been associated with a lack of a laetrile in any animal. Since experimental animals (mice, rats, guinea pigs) have been maintained in good health over a number of generations on synthetic diets of pure chemical components, but containing no laetriles, it is evident that lack of this material is not associated with any disease.[7,8]*
- The tissues of animal bodies contain enzymes that can decompose all of the usual constituents of foodstuffs and thus form decomposition products that can be readily eliminated. The tissues of the body contain such minute amounts of the enzyme beta-glucosidase, the only enzyme that can decompose laetriles, that these compounds probably are not extensively broken down when introduced parenterally and are probably excreted mainly intact in the urine. When ingested by mouth the laetriles are decomposed by beta-glucosidase present in the microbial population of the intestinal tract and the breakdown products are disposed of in a manner normal for each component. This is the reason why the laetriles taken orally are much more poisonous than when injected. It is then that highly poisonous cyanide is liberated.
- One of the fundamental properties of a vitamin is that it has a unique physiological function that can not be performed by any other class of compounds. No evidence has been adduced that laetriles have any such physiological function. The claim that laetriles have the property of a vitamin (so-called vitamin B_{17}) therefore is not supported by any valid scientific evidence.

Other statements of dubious validity have been made in attempting to establish physiological functions for cyanogenic glycosides:

- It has been said that cyanogenic glycosides could account for the thiocyanate of body fluids. This is not a unique property, since any source of cyanide formed in the body (and some are known) can be converted to thiocyanate through the action of rhodanese. For example, it is well known that smoking increases the excretion of thiocyanate.
- It has been stated that cyanogenic glycosides might be the source of the cyanide that goes to the formation of cyanocobalamin. Cyanocobalamin is not the active form of vitamin B_{12}. Actually it is an artifact formed from the physiologically active hydrocobalamin during the isolation of vitamin B_{12}.

The above suggested properties, of course, have no bearing on the alleged vitamin nature of the cyanogenic glycosides since they can be caused by any source of cyanide.

Vitamins and Cancer

Is there some special relationship between vitamins and cancer? There are no valid grounds to believe there is. After many years' search for a unique difference in metabolism between normal and neoplastic cells, none has been found—except for quantitative differences in rates of certain metabolic reactions. Cancer cells, like normal cells, require the known essential nutrients to grow and proliferate. Cells with a high rate of turnover are more susceptible to a nutritional deficiency than nonproliferating or slowly proliferating cells.

The nutritional studies of an earlier period relating to cancer have been reviewed by several writers.[9,10] The induction time of spontaneous mammary carcinomas as well as of certain other tumors in mice was found to be lengthened by dietary restrictions including restriction of certain of the B vitamins. However, this was shown not to be a direct effect, but rather was due to the production of abnormalities in estrogen metabolism.

Deficiency of various vitamins of the B group inhibits growth and may lead to the destruction of rapidly growing neoplasms, as is also true for normal cells. This has been proved most strikingly by the administration of certain vitamin analogues which produce a profound vitamin deficiency by interfering with the normal utilization of the vitamin for its appropriate function.[11-15]

For example, methotrexate (amethopterin), one of the most useful anticancer drugs, exerts its curative effect by interfering with the normal cellular functions of the vitamin folic acid.[11] This analogue is, of course, also toxic to body cells with a high rate of turnover, namely the hema-

*Synthetic diets free of cyanogenic glycosides have been employed in nutritional research for over 40 years. The references given represent only one example of numerous synthetic diets published in nutritional journals.

topoietic system, intestinal mucosa and dermis. By a proper regimen that permits the regeneration of normal, affected tissues, methotrexate is useful in the treatment of a variety of neoplasms.

Other examples of the inhibition of the growth of experimental cancers are by isoriboflavin, an antagonist of riboflavin; deoxypyridoxine, an antagonist of pyridoxine and pyrithiamine, an antagonist of thiamine. These agents have not found use in cancer treatment because there is only a small differential between the toxic action on cancer and normal cells.

Could Cyanide Be a Useful Agent for the Eradication of Cancer?

If cyanide was formed in the body, either through cleavage of amygdalin or by direct administration, would it be expected to have a specific cytotoxic effect on cancer tissue? The answer is no. Dating almost from the beginning of this century experiments have been made on the effects of injecting cyanide into cancer-bearing rodents or of maintaining such animals in an atmosphere containing a fixed concentration of HCN gas.[16-19] Increases in survival time of the treated cancer-bearing animals were observed, but the animals also developed erythema, edema and necrosis of the extremities.[18] The general conclusion was that the effective doses were too close to the lethal dose to be of practical use.[16-19]

Brown et al[20] administered cyanide along with anesthetic to patients with uterine tumors directly to the tumor and observed no improvement.

In experiments that have been carried out with amygdalin, this compound has been administered along with beta-glucosidase. The results have been an increased toxicity with no evidence of improvement of anticancer activity.

Summary

The claim that laetrile (amygdalin) has the properties of a vitamin (so-called vitamin B_{17}) is shown to be false by the normal properties characteristic of vitamins. There is no substantial evidence that any vitamin prevents the development of, or has a beneficial effect in the treatment of neoplasms.

The published literature does not support the assumption that cyanide, presumably liberated on the enzymatic decomposition of laetrile, has a specific action on neoplastic cells.

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Informed
OPINION

Psychiatry Today

ENOCH CALLAWAY, MD, *San Francisco*

ALMOST 20 YEARS AGO the late Ralph Gerard began a talk on "Psychiatry Today" with a story about a minister preaching on the virtues of the church. At the high point in his sermon the preacher swung into full metaphor and said, "So the mother church stands, with one foot rooted firmly in the fertile earth of the holy scriptures and the other raised to Almighty God."

Gerard was referring to psychiatry's ungainly posture which, twenty years ago, was due to the growing gap between neurobiology and psychoanalytically oriented psychology. If 20 years ago psychiatry was being split, today it's being drawn and quartered, for in addition to neurobiology and analytic psychology, which had to be reconciled at that time, we now have social and community psychiatry and, most recently, what I will call the exotic disciplines.

Toward the end of World War II, the classical psychoanalytic approach had come to dominate the field of psychiatry. During the period it remained dominant, it also became relatively stagnant (as is often the case with a dominant dogma), and it's hard to point out major advances in psychoanalytic theory or practice within the past 20 years. The elegant structure of Freudian metapsychology has so far failed to live up to its initial promise as a source of testable hypotheses, although the game may not be over yet.

At the time of Gerard's talk 20 years ago, potent psychologically-active medications had begun to produce a dramatic increase in the importance of neurobiological approaches. Studies of these psychoactive chemicals became a major force in developing modern theories of neurohumoral transmission. Those theories have in their turn given rise to repeated promises, unfortunately still unfulfilled, of a rational psychopharmacology. Psychopharmacology then, like psychoanalysis, has developed an elegant pseudotheoretical basis but remains, in fact, an empirical art.

The social and political approaches have made the greatest inroads in the past ten years. They have claimed an increasing share of the space in major psychiatric journals,[1] but that is far from the most noticeable effect they have had. The most dramatic change in psychiatry in the past five years is the wholesale closing of mental hospitals. Neurobiologists can claim some credit because effective antipsychotic medication has played its part, but more important forces have come from social and political action. Social action psychiatrists are certainly empiricists. On the other hand, their attention to social roles and political rights has resulted in questioning some of the psychiatric treatment mythology.

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Finally, we come to what I have called exotic disciplines. Neurochemistry (psychedelic drugs), physiology (biofeedback), and social events (the hippie movement) all are calling serious scientific and psychiatric attention to what five thousand years of eastern thought has to offer, but so far most of the leading people are neither scientists nor psychiatrists. Examples are Carlos Castaneda, Gurdjieff, the Maharishi Mehesh Yogi and Werner Erhard. The roots of the exotic approaches are religious (using that word in its eastern meaning), but modern justifications are principally empirical ("Try it—you'll like it"). A promise of rational theoretical and scientific integration can be found in the increasing new points of contact between exotic disciplines, neurobiology, psychopharmacology, conditioning, and electrophysiology.

These four aspects of psychiatry can be used to conjure up an image of the blind scholars from the elephant legend.* The first is a traditional analyst with beard, cigar and steel-rimmed glasses, still seated behind his Edwardian couch. The second wears a white coat and is surrounded by all the equipment of modern technology. The third is a young man who may be wearing either a gray flannel suit or peace beads, depending on the group he wants to influence. Last, we have the guru in his saffron robe, leading his disciples into the mystery of primal screams, Gestalt encounters or cosmic consciousness. All are making great promises; each can offer some empirical support for the practices he urges, and none has a comprehensive theoretical basis which provides testable predictions of therapeutic interest. Finally, around this Tower of Babel one finds the working psychiatrists. They deal with problems that individual people bring to them, often trying anything that gives promise of helping so that they can "heal a few, aid more and comfort all."

In short, when we come to the problem of treating people, we have plenty of theories to give our art the pretense of scientific respectability, but basically our theories have little to do with our practice. Usually they serve only as mnemonic devices for our observations, and empiricism remains 90 percent of the game.

The chaotic state of psychiatry today has resulted in certain symptoms. Like most psychiatric symptoms, they serve a purpose. They are understandable, even forgivable, but they must be overcome if growth is to occur.

The most crippling symptom is a kind of intellectual tunnel vision. Each approach tends to develop a narrow view of things that excludes all other approaches. This is encouraged by the temper of the times and today's booming market for oversimplification. As a result, we find classic psychological theorists who see all pathology as a consequence of parent-child relationships. There are some neurobiologically oriented people who loudly proclaim that "the couch is out," and argue that the mind will cure itself of any psychological disorder given good nutrition and healthy brain biochemistry. Social and political pundits are equally in possession of the only answer. They see mental illness as entirely the result of faulty socioeconomic systems, or even as simply a myth perpetrated by the establishment and its medical lackeys. The exotic disciplines are too new to have developed extensive dogma in this country, and indeed some of their exercises—such as the Zen koans—seem designed to exercise mistrust in logical syllogisms. Be that as it may, a few of the American exponents of Transcendental Meditation are already making extravagant claims.

Narrow views spare one from disturbing facts and lead to the construction of grand theories that promise everything to everyone. Behind the baroque theoretical facade of current psychiatric theories there are some empirical rules that work, but each collection of empirical rules is almost obscured by the theoretical overgrowth it stimulates. However, at the points of contact between "schools," the myths and dogmas sometimes become testable.

One of these points of contact has occurred between Skinnerian behavior modification and Freudian analysis. First, consider the Skinnerian approach. This views the brain as a black box, the mind as a trivial epiphenomenon and the social sphere as a big operant-conditioning apparatus. Nevertheless, its theories have generated novel therapeutic approaches. First, however, as an exercise, think how you would fit Skinnerian practices into the outline that I have sketched. Is it neurobiology, as in rats running through mazes to test for psychochemical effects? Is it political-social, as embodied in *Walden Two*[2] or in Ullman's book, *Institution and Outcome*[3]? Is it just disguised analytic psychology? (I have seen a Jungian analyst and an orthodox behavior modi-

*An ancient parable concerns four blind wise men studying an elephant. One scholar touched the tail and said, "The elephant is like a rope"; another, a leg and said "The elephant is like a post." The third touched a flank and said, "The elephant is like a wall." The fourth, at the trunk, said, "You are all lying. The elephant is a kind of snake."

fier approach the same clinical program in embarrassingly similar fashions.) Or is it the entering wedge of the exotic disciplines? Operant conditioning of physiological functions (biofeedback) has played a major role in legitimizing some exotic practices such as yoga and Zen. This could be worked into a multiple-choice exam question that would be no more bizarre than some of the other either/or positions found in contemporary psychiatry.

At the interface between behavior modification and analysis, we find an example of how approaching the mind on a different tack can test an old, apparently untestable theory. Freudian theory postulated that neurotic symptoms in general, and phobias in particular, serve both to discharge and to ward off unconscious conflicts, and so are essential to the patient so long as the conflict remains. Thus, if symptoms were removed without resolving the underlying conflict, other symptoms would have to be substituted. In practice, analysis aimed at resolving conflicts so that if a symptom disappeared, one could assume the conflict was resolved. If the symptom returned, it proved that the conflict was not resolved, and circularly proved the symptom-substitution theory. The Skinnerians, however, with their different bias, have been happily removing phobic symptoms by behavior-modification techniques for some time now. Instead of finding new symptoms arising to replace each removed phobia, they usually found the opposite—an improvement in areas of function not obviously related to the removed phobia.[4]

A point of contact between psychophysiology and learning-theory has led to a new discipline known as biofeedback.[5] Alpha-conditioning is one example that has received considerable popular coverage. A computer gives a person very rapid information (feedback) as to his physiological state so that he can learn (be operantly conditioned) to control that state. The resulting self-induced, altered states of consciousness frequently bear a resemblance to some of the states of consciousness used by the so-called exotic disciplines, and so we also have a point of contact with the exotic approaches, such as Transcendental Meditation.

Modern social psychiatry has emphasized the hazards of having psychiatric patients play the "patient role" as defined in the usual medical and surgical scenario. Both biofeedback and Transcendental Meditation depart considerably from the more traditional medical approaches in that in neither case is the patient really dependent upon someone else for treatment. The patient instead becomes responsible for what happens to him. The teacher of biofeedback and the meditation initiator simply introduce certain relatively simple technical manipulations which the identified patient or client may then use at his own discretion to produce an altered state of consciousness if he so chooses.

I have not seen any formal published reports yet, but a group at the Institute of Living in Connecticut has been carrying on a series of experiments using these techniques, and the rumors are encouraging. A combination of Transcendental Meditation and alpha-biofeedback is being used. The control procedure is the more conventional Jacobsen Progressive Relaxation Technique. This is a much more authoritarian method of achieving relaxation, and it bears a very strong resemblance to hypnosis in that the teacher uses strong suggestion in instructing the subject how to relax. Apparently the exotic techniques produce the best clinical results. Thus we find yet another point of contact, this time between social psychiatry and the exotic approaches, and a major factor may be the healthier social role of the patient permitted by the exotic approaches. The patient is not dependent and receiving treatment, but rather is responsible for himself and for using his own senses to determine whether he is being successful at the task which he has set for himself.

To continue with examples, an unexpected point of contact seems to be developing between the exotic disciplines, neurobiology and Jungian psychoanalysis. Neurobiological studies indicate specialization of the cortex, with special areas playing special roles in particular psychological processes. Recently, electrophysiological studies in normals have added support, since a psychological process presumed to use a given cortical area results in reduced background electroencephalogram (for example, alpha) and increased amplitude of specific event-related potentials (for example, evoked responses) arising from that area.[6] The exotic disciplines have drawn attention to alternative modes of thought and consciousness, and some of these alternative modes are what we might expect if psychological processes were dominated by one of the specialized cortical areas.[7]

Cortical left-right asymmetry provides the best known example. For most of us the left side of our brain not only controls the right side of our

body, but also takes care of sequential, logical thought processes such as language, mathematics and similar propositional functions. The right brain (left body) is, on the other hand, the organ of those more holistic processes that are needed for music, art and intuition. That has been referred to as appositional thought by Bogen.[8] Now in addition to his classification of people into extraverts and introverts, Jung had four psychological types: logical, intuitive, sensation and feeling.[9] Logical clearly is left brain and intuitive is right brain. On far more speculative grounds one might suspect that the anterior half of the brain is more involved with what Jung meant by sensation, and the posterior half with what Jung meant by feeling. Pribram[10] has shown that the frontal cortex is involved with focusing down on sense data (sensation), while posterior areas (parietal and infratemporal cortex) act to sample a broader array of data for more complex evaluation (feeling). Support comes from Picton and Hillyard,[11] who find early anterior brain evoked electrical potential changes associated with stimulus set and, later, more posterior evoked potentials associated with response set.

The anterior/posterior relation to sensation/feeling is much more speculative than the left/right relation to logical/intuitive, but the possibilities are intriguing. Can modern electrophysiology provide convergent data for analytic psychology? If so, both would profit.

For our last set of examples, we will look at some points of contact between molecular neurobiology and some of the social and psychological approaches. If I had to draw a logos for the neurobiology of 1974, it would surely be the so-called National Institutes of Health synapse. This famous diagram shows how one nerve cell sends its chemical messages to another. In the diagram the presynaptic termination of an axon from one neuron is shown synapsing with the postsynaptic dendrite of another neuron. The diagram gives the steps involved when a neurohumoral transmitter acts to carry messages from one cell to another. It shows the uptake of an amino acid by the cell, the enzyme steps that form the transmitter, the way the transmitter acts on the postsynaptic membrane when it is released in the synapse and then how it is removed from the synapse by re-uptake and by various pathways of degradative metabolism so that the system can be ready for another message. Almost all of the drugs that are known to affect the mind also operate on mechanisms of neurohumoral transmission in one way or another, modifying either the metabolism of the neurotransmitters or the various postsynaptic changes that the neurotransmitters produce. We are increasingly able to interfere more or less specifically in various steps of neurohumoral transmission, and this has made neuropharmacology a logical game of great elegance, intellectual challenge and practical reward. For a while it looked like we might be on the verge of powerful answers for clinical psychiatry. Schizophrenia, it seemed, might be due to a defect in the metabolism of the neurotransmitter called dopamine; depression, to a defect in norepinephrine, or perhaps serotonin.

At the point of contact between studies of molecular biology and studies of human behavior, however, things have ceased to look quite so simple. The advent of drugs which literally knock out one or the other of these neurotransmitter systems has shed a great deal of light on some things and confusion on others, for the behavioral effects of some of these chemicals have been surprisingly small. Thus, parachloraphenolalanine (which blocks the serotonergic system) and alpha methyl paratyrosene (which depletes brain dopamine and norepinephrine) have remarkably little effect on humans.[12]

Another part of the story which made us feel that answers might be near at hand for the major psychoses came from the study of metabolites produced by people with major psychoses. Particularly, there were a number of changes in the metabolites of neurohumoral transmitters that occurred in mania and in depression. Just recently Post and Goodwin[13] have reported that volunteer patients who were depressed but who agreed to act as though they were manic, ceased to show the pattern of metabolites characteristic of depression and began to show the pattern of metabolites characteristic of mania during this simulated mania. Although the chemicals changed, there was no concomitant change in the mood or actual clinical state of these simulating patients. Thus we see again that although chemicals can influence the mind, the mind can also influence chemicals.

In the Post and Goodwin studies the subjects only simulated mania for one day. It would be interesting to find out if more prolonged simulation, with subsequent more prolonged effects on neurohumoral transmitters (behaviorally produced in this case), might not indeed have some psychological effect which failed to show up in the one-day experiments carried out so far. We

do not know what would happen to the mind if it were induced to chronically alter its own neurochemical milieu.

To extend this one step further: the sort of socicty that fosters a particular kind of behavior may produce modifications in the neurochemistry of members of that society; and, by the same token, a group of people who inherit a particular neurochemical makeup may form a society which is, in part, molded by their particular neurochemical disposition.

Most clinicians recognize that cause does not necessarily specify treatment. There may indeed be "no twisted thought without a twisted molecule." That molecule, however, may once have been twisted by genetic forces or postconceptual physiological forces, or psychological forces, or more likely some combination. We then may untwist it by using psychological input, physical and chemical input or, again, some combination. Just because the pathological chemical twist was primarily the result of some genetic factor does not mean that it may not be untwisted by some psychological manipulation, or vice versa.

With luck, knowledge about any neuro-biopsychological mechanism may be turned to therapeutic advantage whether or not that mechanism had anything to do with the cause of the disorder. The intellectual trap is to assume that therapeutic success indicates cause (and so supports a narrow, bigoted viewpoint). It is obvious that when an antipsychotic drug given by a neurobiologist helps the schizophrenic, this does not indicate that the schizophrenic was necessarily suffering from a congenital phenothiazine deficiency. It is less obvious that when a disturbed person gets along better after learning from his transactional analyst that his punitive "parent" needs to be brought under the control of his "adult," then it does not necessarily follow that he was disturbed because he actually had a punitive parent.

Psychiatry is by definition a medical specialty concerned with psychological disorders. This implies that as a physician, a psychiatrist should have the ability to accept responsibility for the whole patient, and that either he should be competent in the various disciplines needed to help the patient, or else should know how to orchestrate the nonphysician specialists that are needed to supplement his skills. This is not always the case. The British often make a distinction between physicians and surgeons, refering to surgeons as "Mr." rather than "Dr.," in recognition of the fact that the surgeon may have to limit his overview of the whole patient in order to perfect his particular operative skill. There is a tendency for some psychiatrists to narrow their interests so that they no longer operate as physicians. Again, as in the case of the surgeon, the narrow specialist may go far more deeply into his area than the physician who is always being taxed by the unpredictable needs of human beings. However, I believe that the clinician should take it as his destiny to integrate the discrepant parts that each of the blind wise men gives us.

The challenge is to prevent narrow scholastic provincialism from limiting understanding. The scope of the problem, fairly faced, should lead to some humility. This will contrast with the tactics of the narrow partisans who often erect grandiose schemes that promise everything to everyone, and who end up practically playing God. It is often embarrassing to hear of psychiatrists telling professionals in other fields how to run their affairs on the basis of some wild or tenuous theoretical position. There has been an even more serious consequence, for psychiatry's tendency to oversell and underdeliver has jeopardized its relationship with the rest of medicine.

Did you ever hear a physician say, "I don't believe in ophthalmology," or "I don't believe in dermatology"? Unfortunately, it's quite common to hear one say, "I don't believe in psychiatry." Perhaps that echoes those earlier disappointments with promised omnipotence that find expression in the complaint, "I don't believe in God."

Psychiatry today is a bigoted, polymorph-perverse discipline. Specialists in one arcane division will not talk to those in another. When the clinician draws effective tools from a special discipline, he often takes along some pathetic pseudoscientific theory to sugarcoat the athletic empiricism. So psychiatry is an undisciplined discipline divided by advocates of special techniques. Yet it is in a position to integrate the burgeoning and diverse data on the mind into a more usable fashion, while it tidies up the mess left by its snake-oil salesmen. Oversimplifying opportunists are always ready to cash in on the natural desire of physicians for simple answers, and of sick people for quick cures. However, David Szent Gyorgi once said that nature could not be as complicated as it seems because otherwise it would not work. The austere theoretical structure of behavior modification shows the possibility of a scientific psychiatric therapeutics, limited as it may be. Theoretical

neuropharmacology is so pregnant that some viable therapeutic offspring is bound to arrive soon. The promise of rational and integrative theories arising from the interface of physiology and psychology become increasingly credible. Psychiatry may be on the verge of maturing into an openminded, modest scientifically-based branch of medicine—but it has not just yet.

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Medical Information

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Atherosclerosis Prevention in Children

A Statement of the

CALIFORNIA SOCIETY OF PEDIATRIC CARDIOLOGY

and

CALIFORNIA HEART ASSOCIATION

IT IS ACKNOWLEDGED that atherosclerosis is probably a complex, multifactorial disease which is incompletely understood at this time. The well-known risk factors are also acknowledged to not necessarily represent etiologic factors, but may well be critical links in a pathologic sequence. If risk factors can be modified or reduced without causing harm,[1] this would seem to be desirable in the face of an inevitable delay of several decades before conclusive evidence may be forthcoming. Several risk factors are noted with comment.

• *Elevated serum cholesterol.* This has the highest single correlation with risk of major coronary artery disease. Although average values for our general population are known, they tend to be much higher than in populations in which there is a low incidence of atherosclerosis. Proper or ideal norms are not critically defined for children, but values above 190 to 200 mg per 100 ml are almost certainly excessive for adolescents while levels as low as 160 to 170 mg per 100 ml may be abnormal for infants and small children.[2]

The highest priority and most fruitful area of case finding will be in those children where there is a strong family history of early atherosclerotic heart disease and its complications. There should be a heightened sensitivity to the need to take a detailed and ongoing history of such events in the family. In one study of the offspring of fathers who sustained myocardial infarctions under the age of 41, twenty-one percent of the children had hyperlipoproteinemia.[3]

No firm recommendation can be made at this time regarding routine periodic cholesterol screening of all infants and children. However, an economic and accurate methodology already exists that will allow for cholesterol determination on only .05 ml of serum derived from a finger stick.[4] Further experience and implementation of such techniques may allow for greater screening commitments in the future. Serious question has been raised in the recent literature regarding the value of lipoprotein phenotyping suggesting that whole plasma lipid levels alone may prove more clinically useful.[5]

Epidemiologically, there are no populations which have a low intake of saturated fatty acids and high incidence of coronary artery disease.[6] It has also been shown in several large controlled studies that reduction of serum cholesterol by as little as 12 to 15 percent as late as the fourth and fifth decades significantly reduces the frequency of fatal coronary events.[7] This degree of reduction has been achieved by modest changes in the diet which are in the direction of diets prevailing in simpler cultures with a lower incidence of coronary artery disease. It would seem reasonable to assume that similar changes instituted earlier would have even greater impact.

The exact percentage of the population that has clear-cut genetic or familial hyperlipoproteinemia is not known. Although many persons appear to be "protected," our population as a whole appears to suffer from epidemic hyperlipidemia by international standards.[8] Both in human clinical and primate animal (rhesus monkey) studies, the average American diet is atherogenic while the prudent diet is notably less so with preliminary reports of reversal of lesions in the rhesus monkey with shift to the prudent diet.[9]

It is recommended, therefore, that modest shifts in our dietary pattern be made now for the general population in the hope of achieving optimal benefit for children over their lifetime. These changes in broad terms will require some reduction in protein foods of animal origin (meat, eggs and dairy products) which in turn will reduce the in-

California Society of Pediatric Cardiology, *ad hoc* Committee for Atherosclerosis Prevention: Martin Reisman, MD, Chairman, Robert Stanton, MD, Samuel Sapin, MD, and Ralph Weiss, MD; and California Heart Association, Task Force for Heart Disease in the Young: I. Hunter Crittenden, MD, Chairman, Marvin Auerback, MD, Stanley Kegel, MD, and Mr. Jack Wilmore.

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take of saturated fats and cholesterol. Specifically this will represent an increased use of fish, poultry, lean meat, fruits, vegetables and cereal grains and a de-emphasis of high fat content meat products (sausage and luncheon meats, "premium" fat marbled meats), milk and milk products (skimmed milk excepted), and pastries made with massive amounts of butter and refined sugar. Inasmuch as eating habits and food preferences are established in very early childhood, pediatricians are in an ideal position to help establish optimal dietary guidelines for the young family (parent *and* child). Details of such a prudent diet are available from the American Heart Association.

- *Obesity.* Every effort should be made to alter eating and activity patterns that lead to this increasingly common condition. The ready availability of foods and desserts of high caloric density have contributed to this situation, and a meaningful attempt to alter family eating patterns will be required in addition, ultimately, to a major reorientation of the food processing industry.
- *Smoking.* The role of smoking in causing lung cancer has been well publicized. It further increases by two to three fold the incidence of coronary artery disease.[10] Every effort should be made to discourage the initiation of smoking in the pediatric age range.
- *Hypertension.* Although uncommon in children and adolescents, it is seen with sufficient frequency to warrant a firm commitment to making blood pressure determinations at all routine examinations with proper workup and treatment when discovered.
- *Exercise.* There is no clear proof that regular exercise will prolong life, but it does induce a number of physiological changes that seem favorable, including the potential to minimize obesity, and would therefore seem to be desirable.

There is already evidence that many of the risk factors for adults can be identified in childhood and adolescence. We take the optimistic view (1) that many of the etiologic or contributing factors to the atherosclerotic spectrum may be capable of modification, (2) that some action is indicated now in spite of less than totally conclusive data and (3) that these efforts should be pursued by physicians who care for children and adolescents.

In summary, we recommend:

- A heightened interest in case finding in families with a strongly positive history of arteriosclerotic heart disease and its complications. Case finding in children may be greatly facilitated by better communication between cardiologists and internists caring for adults and physicians caring for children in higher risk families. Routine cholesterol screening of all infants and children cannot be firmly recommended at this time but should probably be considered as soon as economically and practically feasible.
- A greater commitment to nutritional counseling along with promotion of regular exercise aimed at minimizing obesity and hyperlipidemia in the general population. Grossly elevated serum lipids should be treated with institution of appropriate dietary or drug management or both and ongoing follow-up.
- Increased efforts to take blood pressure reading routinely in children and adolescents at the time of annual physical examinations.
- Continuing and vigorous efforts to discourage smoking.

The above mentioned risk factors and recommendations are by no means meant to represent a comprehensive review of the subject. There are a very large number of additional proposed contributing factors to the atherosclerotic process that have either been hypothesized or are partially supported by experimental or epidemiological studies. Many of these factors are environmental or related to diet or food processing and would lend themselves to modification if further studies prove them to be of major importance. Continuing research is most urgently needed and endorsed.

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in memoriam

BEAM, MARK P., Newport Beach. Died November 15, 1974 in Newport Beach of cancer of the larnyx, aged 77. Graduate of the University of Colorado School of Medicine, Denver, 1926. Licensed in California in 1947. Dr. Beam was a member of the Los Angeles County Medical Association.

BENNETT, JOHN FRANCIS, San Leandro. Died February 11, 1975 in San Leandro of cancer of the lung and pneumonia, aged 88. Graduate of the University of Illinois College of Medicine, Chicago, 1916. Licensed in California in 1955. Dr. Bennett was a retired member of the Alameda-Contra Costa Medical Association.

BLOMGREN, STEPHEN EMMANUEL, La Jolla. Died February 19, 1975 in La Jolla, aged 39. Graduate of the University of Rochester School of Medicine and Dentistry, 1962. Licensed in California in 1970. Dr. Blomgren was a member of the San Diego County Medical Society.

BRANCH, WILLIAM EDWARD, Los Angeles. Died February 19, 1975 in Altadena, aged 80. Graduate of the University of Texas School of Medicine, Galveston, 1923. Licensed in California in 1923. Dr. Branch was a member of the Los Angeles County Medical Association.

CASADY, RICHARD ROBBINS, Los Angeles. Died December 29, 1974 of cerebrovascular accident, aged 59. Graduate of the University of Southern California School of Medicine, Los Angeles, 1945. Licensed in California in 1945. Dr. Casady was a member of the Los Angeles County Medical Association.

COSTLEY, E. CHRISTINE, Pasadena. Died November 3, 1974 in Pasadena of heart disease, aged 54. Graduate of Western Reserve University School of Medicine, Cleveland, 1958. Licensed in California in 1962. Dr. Costley was an associate member of the Los Angeles County Medical Association.

EFNER, WILLIAM D., El Toro. Died August 13, 1974 in Palm Springs of cancer of the intestine and liver, aged 68. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1931. Licensed in California in 1931. M.D. degree from California College of Medicine, 1962. Dr. Efner was a retired member of the Los Angeles County Medical Association.

GAYNES, HARVEY E., Encino. Died December 5, 1974 in Santa Monica of acute pancreatitis, aged 64. Graduate of the University of Illinois College of Medicine, Chicago, 1936. Licensed in California in 1944. Dr. Gaynes was a member of the Los Angeles County Medical Association.

GOLDMAN, LEON, San Francisco. Died March 4, 1975 in San Francisco, aged 71. Graduate of the University of California Medical School, Berkeley-San Francisco, 1930. Licensed in California in 1930. Dr. Goldman was a member of the San Francisco Medical Society.

GRUNECK, FREDERICK, Northridge. Died January 30, 1975 in Northridge, aged 77. Graduate of Medizinische Fakultät der Universität, Wien, 1921. Licensed in California in 1929. Dr. Gruneck was a member of the Los Angeles County Medical Association.

HAEREM, ALF T., Redwood City. Died February 15, 1975 in La Jolla of heart disease, aged 62. Graduate of the University of Chicago School of Medicine, 1937. Licensed in California in 1946. Dr. Haerem was a member of the San Mateo County Medical Society.

HAGEN, KENNETH R., Fresno. Died February 7, 1975, aged 67. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1932. Licensed in California in 1932. Dr. Hagen was a retired member of the Fresno County Medical Society.

HOLLEY, WALLACE WILLIAM, Inglewood. Died January 27, 1975 in Brawley, aged 84. Graduate of the University of Minnesota Medical School, Minneapolis, 1917. Licensed in California in 1924. Dr. Holley was a member of the Los Angeles County Medical Association.

KIMBER, JAMES H., San Bernardino. Died January 6, 1975 in Hemet, aged 64. Graduate of Syracuse University College of Medicine, 1941. Licensed in California in 1946. Dr. Kimber was a member of the San Bernardino County Medical Society.

MACKENZIE, RONALD JOHN, Long Beach. Died February 11, 1975 in Long Beach, aged 50. Graduate of McGill University Faculty of Medicine, Montreal, 1948. Licensed in California in 1950. Dr. MacKenzie was a member of the Los Angeles County Medical Association.

MCNAMARA, DELBERT H., Santa Barbara. Died February 13, 1975 in Santa Barbara, aged 71. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1929. Licensed in California in 1929. Dr. McNamara was a retired member of the Santa Barbara County Medical Society.

MILLER, RALPH FLOYD, Bakersfield. Died November 14, 1974 in Bakersfield of cerebral thrombosis, aged 89. Graduate of the Hahnemann Medical College and Hospital, Chicago, 1909. Licensed in California in 1924. Dr. Miller was a retired member of the Los Angeles County Medical Association.

MULVEHILL, WALTER WILLIAM, Beverly Hills. Died January 18, 1975 in Beverly Hills of osteoarthritis, aged 84. Graduate of College of Physicians and Surgeons, Medical Department, University of Southern California, 1915. Licensed in California in 1915. Dr. Mulvehill was a member of the Los Angeles County Medical Association.

NEVILLE, JOHN EDWARD, Glendale. Died January 17, 1975 in Glendale of heart disease and cancer of the pancreas, aged 79. Graduate of the University of Texas School of Medicine, Galveston, 1922. Licensed in California in 1923. Dr. Neville was a member of the Los Angeles County Medical Association.

O'CONNOR, JOSEPH PATRICK, Pasadena. Died February 2, 1975 in Pasadena of cancer of the stomach, aged 72. Graduate of Creighton University School of Medicine, Omaha, 1932. Licensed in California in 1932. Dr. O'Connor was a member of the Los Angeles County Medical Association.

PAUL, OLIN, Solvang. Died December 11, 1974 in Santa Barbara of cerebrovascular accident and pneumonia, aged 75. Graduate of the University of Ottawa Faculty of Medicine, Ottawa, 1924. Licensed in California in 1929. Dr. Paul was a retired member of the Los Angeles County Medical Association.

PELUSO, JOSEPH D., Los Angeles. Died January 21, 1975 in Los Angeles of cerebrovascular accident, aged 80. Graduate of Fordham University School of Medicine, New York, 1918. Licensed in California in 1923. Dr. Peluso was a member of the Los Angeles County Medical Association.

PHILLIPS, MILTON CHARLES, Fullerton. Died in January 1975, aged 43. Graduate of the University of Wisconsin Medical School, Madison, 1957. Licensed in California in 1958. Dr. Phillips was a member of the Orange County Medical Association.

SCHAUPP, KARL L., SR., San Francisco. Died March 2, 1975 in Ross, aged 92. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1916. Licensed in California in 1916. Dr. Schaupp was a past president of the California Medical Association and of the San Francisco Medical Society, and a retired member of the San Francisco Medical Society.

SIMMERS, MAURICE HOLMES, Los Angeles. Died September 22, 1974 in Pasadena of heart disease, aged 72. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1937. Licensed in California in 1937. M.D. degree from California College of Medicine, 1962. Dr. Simmers was an associate member of the Los Angeles County Medical Association.

SMITH, ALBERT THOMAS, Sonoma. Died February 5, 1975 in Sonoma County of injuries received in an automobile accident, aged 36. Graduate of the Ohio State University College of Medicine, Columbus, 1965. Licensed in California in 1966. Dr. Smith was a member of the Sonoma County Medical Association.

STANTON, JAMES ROBERT, Santa Clara. Died February 7, 1975 in Santa Clara of cancer, aged 44. Graduate of Indiana University School of Medicine, Bloomington-Indianapolis, 1955. Licensed in California in 1956. Dr. Stanton was a member of the Santa Clara County Medical Society.

STURCHIO, LAWRENCE E., Inglewood. Died February 3, 1975 in Anaheim of heart disease and diabetes mellitus, aged 60. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1946. Licensed in California in 1946. M.D. degree from California College of Medicine, 1962. Dr. Sturchio was a member of the Los Angeles County Medical Association.

WARD, GEORGE HUGH, Van Nuys. Died November 23, 1974 in Van Nuys of brain tumor, aged 67. Graduate of the University of Pittsburgh School of Medicine, 1939. Licensed in California in 1949. Dr. Ward was a member of the Los Angeles County Medical Association.

ZANTINY, WILLIAM GEORGE, JR., Long Beach. Died February 19, 1975 in Long Beach of metastatic carcinoma of the pancreas, aged 61. Graduate of Western Reserve University School of Medicine, Cleveland, 1941. Licensed in California in 1947. Dr. Zantiny was a member of the Los Angeles County Medical Association.

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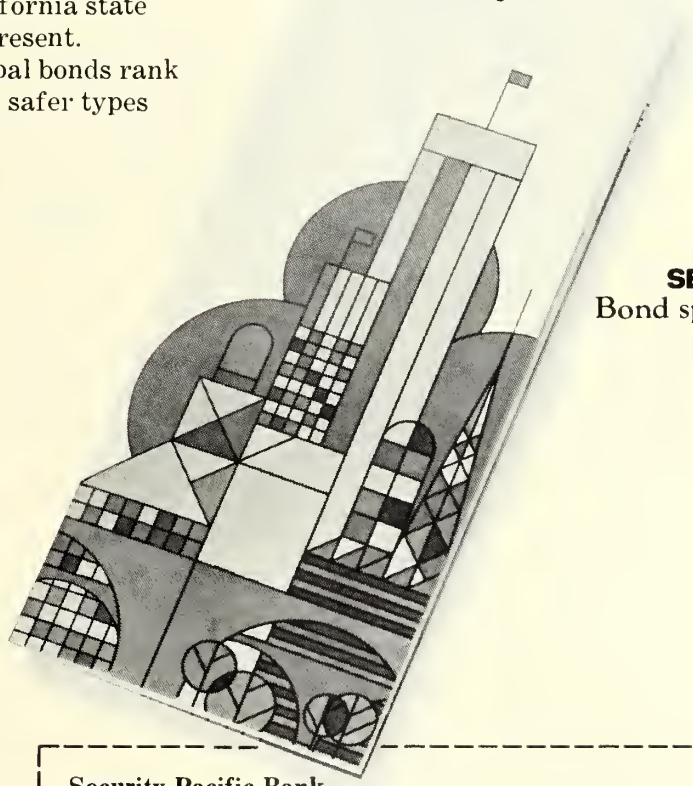

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"Probably" effective: For estrogen deficiency-induced osteoporosis, and only when used in conjunction with other important therapeutic measures such as diet, calcium, physiotherapy, and good general health-promoting measures. Final classification of this indication requires further investigation.

Contraindications: Short acting estrogens are contraindicated in patients with (1) markedly impaired liver function; (2) known or suspected carcinoma of the breast, except those cases of progressing disease not amenable to surgery or irradiation occurring in women who are at least 5 years postmenopausal; (3) known or suspected estrogen-dependent neoplasia, such as carcinoma of the endometrium; (4) thromboembolic disorders, thrombophlebitis, cerebral embolism, or in patients with a past history of these conditions; (5) undiagnosed abnormal genital bleeding.
Warnings: Estrogen therapy should not be given to women with recurrent chronic mastitis or abnormal mammograms except, if in the opinion of the physician, it is warranted despite the possibility of aggravation of the mastitis or stimulation of undiagnosed estrogen-dependent neoplasia.

The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, retinal thrombosis, cerebral embolism and pulmonary embolism). If these occur or are suspected, estrogen therapy should be discontinued immediately.

Estrogens may be excreted in the mother's milk and an estrogenic effect upon the infant has been described. The long range effect on the nursing infant cannot be determined at this time.

Hypercalcemia may occur in as many as 15 percent of breast cancer patients with metastases, and this usually indicates progression of bone metastases. This occurrence depends neither on dose nor on immobilization. In the presence of progression of the cancer or hypercalcemia, estrogen administration should be stopped.

A statistically significant association has been reported between maternal ingestion of diethylstilbestrol during pregnancy and the occurrence of vaginal carcinoma in the offspring. This occurred with the use of diethylstilbestrol for the treatment of threatened abortion or high risk pregnancies. Whether or not such an association is applicable to all estrogens is not known at this time. In view of this finding, however, the use of any estrogen in pregnancy is not recommended.

Failure to control abnormal uterine bleeding or unexpected recurrence is an indication for curettage.
Precautions: As with all short acting estrogens, the following precautions should be observed:

A complete pretreatment physical examination should be performed with special reference to pelvic and breast examinations.

To avoid prolonged stimulation of the endometrium and breasts in climacteric or hypogonadal women, estrogens should be administered cyclically (3 week regimen with 1 week rest period—withdrawal bleeding may occur during rest period).

Because of individual variation in endogenous estrogen production, relative overdosage may occur which could cause undesirable effects such as abnormal or excessive uterine bleeding, mastodynia and edema.

Because of salt and water retention associated with estrogenic anabolic activity, estrogens should be used with caution in patients with epilepsy, migraine, asthma, cardiac, or renal disease.

If unexplained or excessive vaginal bleeding should occur, reexamination should be made for organic pathology.

Pre-existing uterine fibromyomata may increase in size while using estrogens; therefore, patients should be examined at regular intervals while receiving estrogenic therapy.

The pathologist should be advised of estrogen therapy when relevant specimens are submitted.

Because of their effects on epiphyseal closure, estrogens should be used judiciously in young patients in whom bone growth is incomplete.

Prolonged high dosages of estrogens will inhibit anterior pituitary functions. This should be borne in mind when treating patients in whom fertility is desired.

The age of the patient constitutes no absolute limiting factor, although treatment with estrogens may mask the onset of the climacteric.

Certain liver and endocrine function tests may be affected by exogenous estrogen administration. If test results are abnormal in a patient taking estrogen, they should be repeated after estrogen has been withdrawn for one cycle.
Adverse Reactions: The following adverse reactions have been reported associated with short acting estrogen administration:
nausea, vomiting, anorexia
gastrointestinal symptoms such as abdominal cramps and bloating
breakthrough bleeding, spotting, unusually heavy withdrawal bleeding (See DOSAGE AND ADMINISTRATION)
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reactivation of endometriosis
possible diminution of lactation when given immediately postpartum
loss of libido and gynecomastia in males
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change in body weight (increase, decrease)
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If the patient has not menstruated within the last two months or more, cyclic administration is started arbitrarily. If the patient is menstruating, cyclic administration is started on day 5 of bleeding. If breakthrough bleeding (bleeding or spotting during estrogen therapy) occurs, increase estrogen dosage as needed to stop bleeding. In the following cycle, employ the dosage level used to stop breakthrough bleeding in the previous cycle. In subsequent cycles, the estrogen dosage is gradually reduced to the lowest level which will maintain the patient symptom-free.

Postmenopause—as a protective measure against estrogen deficiency-induced degenerative changes (*e.g.* osteoporosis, atrophic vaginitis, kraurosis vulvae)—0.3 mg. to 1.25 mg. daily and cyclically. Adjust dosage to lowest effective level.

Osteoporosis (to retard progression)—usual dosage 1.25 mg. daily and cyclically.

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CONTRAINDICATIONS: Central nervous system depression from drugs (barbiturates, alcohol, narcotics, analgesics, antihistamines); bone marrow depression; known hypersensitivity to phenothiazines or amitriptyline. Do not give concomitantly with MAOI drugs because hyperpyretic crises, severe convulsions, and deaths have occurred from such combinations. Allow minimum of 14 days between therapies, then initiate therapy with TRIAVIL cautiously, with gradual increase in dosage until optimum response is achieved. Not recommended for use during acute recovery phase following myocardial infarction.

WARNINGS: TRIAVIL should not be given with guanethidine or similarly acting compounds. Use cautiously in patients with history of urinary retention, angle-closure glaucoma, increased intraocular pressure, or convulsive disorders. In patients with angle-closure glaucoma, even average doses may precipitate an attack. Patients with cardiovascular disorders should be watched closely. Tricyclic antidepressants, including amitriptyline HCl, particularly in high doses, have been reported to produce arrhythmias, sinus tachycardia, and prolongation of conduction time. Myocardial infarction and stroke have been reported with tricyclic antidepressant drugs. Close supervision is required for hyperthyroid patients or those receiving thyroid medication. Caution patients performing hazardous tasks, such as operating machinery or driving motor vehicles, that drug may impair mental and/or physical abilities. Not recommended in children or during pregnancy.

PRECAUTIONS: Suicide is a possibility in depressed patients and may remain until significant remission occurs. Such patients should not have access to large quantities of this drug.

Perphenazine: Should not be used indiscriminately. Use with caution in patients who have previously exhibited severe adverse reactions to other phenothiazines. Likelihood of untoward actions is greater with high doses. Closely supervise with any dosage. The antiemetic effect of perphenazine may obscure signs of toxicity due to overdosage of other drugs or make more difficult the diagnosis of disorders such as brain tumor or intestinal obstruction. A significant, not otherwise explained, rise in body temperature may suggest individual intolerance to perphenazine, in which case discontinue.

If hypotension develops, epinephrine should not be employed, as its action is blocked and partially reversed by perphenazine. Phenothiazines may potentiate the action of central nervous system depressants (opiates, analgesics, antihistamines, barbiturates, alcohol) and atropine. In concurrent therapy with any of these, TRIAVIL should be given in reduced dosage. May also potentiate the action of heat and phosphorous insecticides.

Amitriptyline: In manic-depressive psychosis, depressed patients may experience a shift toward the manic phase if they are treated with an antidepressant. Patients with paranoid symptomatology may have an exaggeration of such symptoms. The tranquilizing effect of TRIAVIL seems to reduce the likelihood of this effect. When amitriptyline HCl is given with anticholinergic agents or sympathomimetic drugs, including epinephrine combined with local anesthetics, close supervision and careful adjustment of dosages are required.

Caution is advised if patients receive large doses of ethchlorvynol concurrently. Transient delirium has been reported in patients who were treated with 1 g of ethchlorvynol and 75-150 mg of amitriptyline HCl

Amitriptyline HCl may enhance the response to alcohol and the effects of barbiturates and other CNS depressants.

Concurrent administration of amitriptyline HCl and electroshock therapy may increase the hazards associated with such therapy. Such treatment should be limited to patients for whom it is essential. Discontinue several days before elective surgery if possible. Elevation and lowering of blood sugar levels have both been reported.

ADVERSE REACTIONS: Similar to those reported with either constituent alone.

Perphenazine: Side effects may be any of those reported with phenothiazine drugs: extrapyramidal symptoms (opisthotonus, oculogyric crisis, hyperreflexia, dystonia, akathisia, acute dyskinesia, ataxia, parkinsonism) can usually be controlled by the concomitant use of effective antiparkinsonian drugs and/or by reduction in dosage, but sometimes persist after discontinuation of the phenothiazine.

Tardive dyskinesia may appear in some patients on long-term therapy or may occur after drug therapy with phenothiazines and related agents has been discontinued. The risk appears to be greater in elderly patients on high-dose therapy, especially females. Symptoms are persistent and in some patients appear to be irreversible. The syndrome is characterized by rhythmical involuntary movements of the tongue, face, mouth, or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Involuntary movements of the extremities sometimes occur. There is no known treatment for tardive dyskinesia; antiparkinsonism agents usually do not alleviate the symptoms. It is advised that all antipsychotic agents be discontinued if the above symptoms appear. If treatment is reinstituted, or dosage of the particular drug increased, or another drug substituted, the syndrome may be masked. It has been suggested that fine vermicular movements of the tongue may be an early sign of the syndrome, and that the full-blown syndrome may not develop if medication is stopped when lingual vermiculation appears.

Other side effects are skin disorders (photosensitivity, itching, erythema, urticaria, eczema, up to exfoliative dermatitis); other allergic reactions (asthma, laryngeal edema, angioneurotic edema, anaphylactoid reactions); peripheral edema; reversed epinephrine effect; hyperglycemia; endocrine disturbances (lactation, galactorrhea, gynecomastia, disturbances of menstrual cycle); altered cerebrospinal fluid proteins; paradoxical excitement; hypertension, hypotension, tachycardia, and ECG abnormalities (quinidine-like effect); reactivation of psychotic processes; catatonic-like states; autonomic reactions, such as dry mouth or salivation, headache, anorexia, nausea, vomiting, constipation, obstipation, urinary frequency or incontinence, blurred vision, nasal congestion, and a change in pulse rate; hypnotic effects; pigmentary retinopathy; corneal and lenticular pigmentation; occasional lassitude, muscle weakness, mild insomnia. Other adverse reactions reported with various phenothiazine compounds include blood dyscrasias (pancytopenia, thrombocytopenic purpura, leukopenia, agranulocytosis, eosinophilia); liver damage (jaundice, biliary stasis); grand mal convulsions; cerebral edema; polyphagia; photophobia; skin pigmentation; and failure of ejaculation.

Amitriptyline: Note: Listing includes a few reactions not reported for this drug, but which have occurred with other pharmacologically similar tricyclic antidepressant drugs. *Cardiovascular:* Hypotension; hypertension; tachycardia; palpitation; myocardial infarction; arrhythmias; heart block; stroke. *CNS and Neuromuscular:* Confusional states; disturbed concentration; disorientation; delusions; hallucinations; excitement; anxiety; restlessness; insomnia; nightmares; numbness, tingling, and paresthesias of the extremities; peripheral neuropathy; incoordination; ataxia; tremors; seizures; alteration in EEG patterns; extrapyramidal symptoms; tinnitus. *Anticholinergic:* Dry mouth; blurred vision; disturbance of accommodation; constipation; paralytic ileus; urinary retention; dilatation of urinary tract. *Allergic:* Skin rash; urticaria; photosensitization; edema of face and tongue. *Hematologic:* Bone marrow depression including agranulocytosis; leukopenia; eosinophilia; purpura; thrombocytopenia. *Gastrointestinal:* Nausea; epigastic distress; vomiting; anorexia; stomatitis; peculiar taste; diarrhea; parotid swelling; black tongue. *Endocrine:* Testicular swelling and gynecomastia in the male; breast enlargement and galactorrhea in the female; increased or decreased libido; elevated or lowered blood sugar levels. *Other:* Dizziness, weakness; fatigue; headache; weight gain or loss; increased perspiration; urinary frequency; mydriasis; drowsiness; jaundice; alopecia. *Withdrawal Symptoms:* Abrupt cessation after prolonged administration may produce nausea, headache, and malaise. These are not indicative of addiction.

OVERDOSAGE: All patients suspected of having taken an overdosage should be admitted to a hospital as soon as possible. Treatment is symptomatic and supportive. However, the intravenous administration of 1-3 mg of physostigmine salicylate has been reported to reverse the symptoms of tricyclic antidepressant poisoning. On this basis, in severe overdosage with perphenazine-amitriptyline combinations, symptomatic treatment of central anticholinergic effects with physostigmine salicylate should be considered.

For more detailed information, consult your MSD Representative or see full Prescribing Information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, Pa 19486.

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CONTINUING MEDICAL EDUCATION

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CALIFORNIA and HAWAII

COMMITTEE ON CONTINUING MEDICAL EDUCATION

THIS BULLETIN of information regarding continuing education programs and meetings of various medical organizations in **California and Hawaii** is supplied by the Committee on Continuing Medical Education of the California Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Committee on Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103; or phone (415) 777-2000. Note: Please see **California Medicine**, Vol. 117, No. 4, October, 1972 issue for a list of organizations approved for Category I Credit toward the CMA Certificate in Continuing Medical Education.

ALCOHOLISM AND DRUG ABUSE

April 25-26—**New Developments in Drug and Alcohol Abuse: Prevention, Treatment and Rehabilitation.** UC, Riverside. Friday-Saturday. Contact: University of California Extension, Riverside 92502. (714) 787-4105.

CANCER

May 7—**American Society of Clinical Oncology.** Town and Country Hotel, San Diego. Wednesday. Contact: Audrey E. Evans, MD, Children's Hospital of Philadelphia, 3400 Civic Ctr. Blvd., Philadelphia, Pa. 19104. (215) 387-6000.

May 8-10—**American Association for Cancer Research, Inc.—66th Annual Meeting.** Town and Country Hotel, San Diego. Thursday-Saturday. Contact: Hugh J. Creech, MD, AACR, 7701 Burholme Ave., Fox Chase, Philadelphia, Pa. 19111. (215) 342-1000, ext. 420.

May 28-30—**Cancer. USC.** Wednesday-Friday.

August 21-22—**Multidisciplinary Approach to Cancer Treatment.** UCSF at Children's Hospital, San Francisco. Thursday-Friday.

MEDICINE

April 15-18—**Consultants' Course in Dermatology.** UCSF. Tuesday-Friday.

April 21-25—**Diagnostic and Therapeutic Skills in Internal Medicine.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. Monday-Friday.

April 23—**Symposium on Cardiovascular Disease—15th Annual.** Calif. Heart Association and N. T. Enloe Memorial Hospital at Elks Lodge Hall, Chico. Wednesday. 6 hrs. $25. Contact: Marge Herman, CHA, 1372 Longfellow Ave., Chico 95926. (916) 342-4247.

April 23—**Cardiology Pulmonary Resuscitation.** DREW at Martin Luther King Hospital, Los Angeles. Wednesday.

April 23-25—**Diabetes and Related Endocrine Diseases.** UCSF. Wednesday-Friday.

April 28—**Cardiology Pulmonary Resuscitation.** DREW at Martin Luther King Hospital, Los Angeles. Monday.

May 2—**The Thyroid.** PMC at Miyako Hotel, San Francisco. Friday. $80.

May 8—**Asthma.** USC. Thursday.

May 8-10—**Heart Disease: Its Causes and Probable Means of Prevention.** UC, Riverside. Thursday-Saturday. Contact: University of California Extension, Riverside 92502. (714) 787-4105.

May 9-10—**Blood Transfusion—1975.** UCSF. Friday-Saturday.

May 9-10—**Rheumatology Symposium.** Letterman Army Medical Center, San Francisco. Friday-Saturday. Contact: Gary S. Hoffman, MD, CPT, MC, Chief, Rheumatology, Letterman Army Medical Center, Presidio of San Francisco 94129.

May 15-16—**American Heart Association, California Affiliate.** Del Monte Hyatt House, Monterey. Thursday-Friday. Contact: Marilyn Probst, Admin. Asst., AHA, Calif. Affiliate, 1370 Mission St., San Francisco 94103. (415) 626-0123.

May 19-23.—**Advances in Internal Medicine.** UCSF. Monday-Friday.

May 22-24—**Ischemic Heart Disease: A Critical Overview.** PMC and American College of Cardiology at St. Francis Hotel, San Francisco. Thursday-Saturday.

May 31—**Head and Spinal Cord Injuries.** See Surgery, May 31.

June 4-7—**Core Curriculum in Echocardiography: New Developments in Cardiac Ultrasound.** American College of Cardiology at Town and Country Hotel, San Diego. Wednesday-Saturday. Contact: Mary Anne McInerny, Dir., Dept. of Cont. Ed. Programs, 9650 Rockville Pike, Bethesda, Md., 20014. (301) 530-1600.

KEY TO ABBREVIATIONS AND SYMBOLS

Medical Centers and CMA Contacts for Information

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103. (415) 777-2000.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Duane Dillman, PhD, Director, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 564-5911, ext. 391.

LLU: Loma Linda University
Contact: John E. Peterson, MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311.

PMC: Pacific Medical Center
Contact: Allen J. Enelow, MD, Chairman, Education Committee, Pacific Medical Center, P.O. Box 7999, San Francisco 94120. (415) 563-4321.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Neil C. Andrews, MD, Chairman, Department of Postgraduate Medicine, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, California College of Medicine, Irvine
Contact: Robert Combs, MD, Associate Dean, Continuing Medical Education, University of California, Irvine—California College of Medicine, Irvine 92664. (714) 833-5991.

UCLA: University of California, Los Angeles
Contact: Donald Brayton, MD, Director Continuing Education in Medicine and the Health Sciences. P.O. Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: Richard A. Lockwood, MD, Associate Dean for Health Manpower, 1310 Basic Sciences Building, University of California, San Diego, School of Medicine, La Jolla 92037. (714) 453-2000, ext. 1251.

UCSF: University of California, San Francisco
Contact: Malcolm S. M. Watts, MD, Associate Dean and Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-2342.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 226-2047.

July 21-24—**Primary Care Dermatology.** STAN. Monday-Thursday.

MENTAL RETARDATION

April 29-30—**Mental Retardation.** USC. Tuesday-Wednesday.

OBSTETRICS AND GYNECOLOGY

April 16-18—**Association of Planned Parenthood Physicians.** See Of Interest to All, April 16-18.

April 21-25—**Family Planning.** UCLA. Monday-Friday. Contact: Irvin M. Cushner, MD, Ob-Gyn Dept., UCLA Center for Health Sciences, Los Angeles 90024. (213) 825-1046.

May 16-17—**Obstetrics and Gynecology Symposium.** Southern Calif. Permanente Medical Group at Sheraton Hotel, Anaheim. Friday-Saturday. Contact: Shirley Gach, So. Calif. Permanente Medical Group, 4900 Sunset Blvd., Los Angeles 90027. (213) 667-4242.

May 16-17—**Academic and Practical Application of Laparoscopy.** UCLA. Friday-Saturday.

May 19-22—**Ob/Endocrinology and Infertility.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. Monday-Thursday.

June 13—**Prematurity Conference.** See Pediatrics, June 13.

PEDIATRICS

April 21-25—**Review of Pediatrics.** USC. Monday-Friday.

April 26—**Growth to Maturity: The Adolescent and the Helping Professions.** UCSF. Saturday.

May 2-3—**Pediatric Symposium.** Southern Calif. Permanente Medical Group. Friday-Saturday. Contact: Shirley Gach, So. Calif. Permanente Medical Group, 4900 Sunset Blvd., Los Angeles 90027. (213) 667-4242.

May 8-10—**Annual Pediatric Course.** UCSF. Thursday-Saturday.

May 16-18—**American Academy of Pediatrics, Northern California Chapter.** Ahwahnee Hotel, Yosemite. Friday-Sunday. Contact: Melvin Schwartz, MD, 2219 Santa Clara Ave., Alameda 94501. (415) 523-3417.

May 17-18—**Hypertension in Children and Adolescents: Facts, Fictions and Controversies.** Memorial Hosp. Med. Ctr. of Long Beach, Children's Hosp. of Long Beach, Children's Hosp. of Los Angeles at Center for Health Education, Long Beach. Saturday-Sunday. Contact: Executive Secretary, Center for Health Education, 2801 Atlantic Ave., Long Beach 90801.

May 18-21—**Heart and Lung Disease in Neonates and Infants.** UCLA at Ahwahnee Hotel, Yosemite. Sunday-Wednesday.

May 31-June 1—**Attentional Disorders in Children.** UCLA at Asilomar Conference Grounds, Monterey. Saturday-Sunday.

June 13—**Prematurity Conference—14th Annual.** STAN. Friday.

July 1-3—**Thirty Grams of Prevention—Annual Pediatric Seminar.** Children's Hospital and Health Center, San Diego, at Hotel del Coronado, Coronado. Tuesday-Thursday. 16 hrs. $30. Contact: Mrs. Franci Perkins, Sec. to Med. Dir., Children's Hospital and Health Center, 8001 Frost St., San Diego 92123. (714) 277-5808, ext. 351.

PSYCHIATRY

April 25—**Prevention and Indirect Services.** See Of Interest to All, April 25.

April 30-May 4—**American Psychoanalytic Association.** Beverly Hilton Hotel, Beverly Hills. Wednesday-Sunday. Contact: Helen Fischer, Exec. Sec., APA, 1 E. 57th St., New York 10022.

May 3-4—**American Society for Adolescent Psychiatry—Annual Meeting.** Century Plaza Hotel, Los Angeles. 9 hrs. $25 for members; $35, non-members. Contact: Mary D. Staples, ASAP, 24 Green Valley Rd., Wallingford, Pa. 19086. (215) 566-1054.

May 4—**American Academy of Psychiatry and the Law—Semi-Annual Meeting.** Anaheim. Sunday. Contact: Seymour Pollack, MD, USC Institute of Psychiatry and Law, 1237 N. Mission Rd., Los Angeles 90033.

May 5-9—**American Psychiatric Association.** Anaheim. Monday-Friday. Contact: Melvin Sabshin, MD, Med. Dir., APA, 1700 18th St., N.W., Washington, D.C. 20009.

May 17—**Suicide Prevention.** UCSF. Saturday.

May 21-26—**Psychiatric Update—2nd Annual.** UCLA at Ahwahnee Hotel, Yosemite. Wednesday-Monday.

May 31-June 1—**Attentional Disorders in Children.** See Pediatrics, May 31-June 1.

June 1-4—**Biofeedback.** UCLA at Asilomar Conference Grounds, Pacific Grove. Sunday-Wednesday.

June 23-27—**Comparative Psychotherapies.** USC at The Waystation, Lake Tahoe. Monday-Friday. 21 hrs. $150. Contact: Donald H. Naftulin, MD, Dir., Cont. Ed. in Psych., USC. (213) 226-2114.

July 26-27—**A Biofeedback Workshop.** UC, Santa Cruz. Saturday-Sunday. 15 hrs. $75. Contact: Darla Chadima, Cont. Ed. Specialist, Applied Sciences Bldg., UC Extension, Santa Cruz 95064. (408) 429-2971.

RADIOLOGY AND PATHOLOGY

April 29-May 6—**Association of University Radiologists.** Vacation Village, San Diego. One week. Contact: Ms. Sheila McGing, Exec. Sec., AUR, 20 N. Wacker Dr., Chicago 60606; or Elliott Lasser, MD, Chr., Radiology Dept., UCSD. (714) 294-6633.

May 3—**Nuclear Medicine—5th Annual Spring Symposium.** Sierra Valley Nuclear Medicine Assn.; No. Calif. Chapter, Society of Nuclear Medicine, at El Rancho Hotel, West Sacramento. Saturday. Contact: Darleen Nelson, Nuclear Med. Dept., Mercy San Juan Hospital, 6501 Coyle Ave., Carmichael 95608.

June 4-7—**Core Curriculum in Echocardiography: New Developments in Cardiac Ultrasound.** See Medicine, June 4-7.

SURGERY AND ANESTHESIOLOGY

April 19—**Surgical and Clinical Anatomy of the Vascular System.** International College of Surgeons, U.S. Section, at L.A. Orthopaedic Hospital, Los Angeles. Saturday. 8 hrs. $50. Contact: Irving Rehman, PhD, Chr., Postgraduate and Ongoing Education Committee, International College of Surgeons, U.S. Section, 5153 Tampa Ave., Tarzana 91356. (213) 344-3305.

April 26-May 3—**Management of the Surgical Patient.** STAN at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week.

April 30-May 3—**Body Contouring and Reconstruction.** UCLA. Wednesday-Saturday.

May 2-3—**Microsurgery of the Anterior Segment of the Eye—6th Annual Jules Stein Lecture and Postgraduate Seminar.** UCLA. Friday-Saturday.

May 2-3—**Trauma.** UCSF at Mary's Help Hospital, San Francisco. Friday-Saturday.

May 4-8—**American Society of Colon and Rectal Surgeons.** Hilton Hotel, San Francisco. Sunday-Thursday. 20 hrs. Contact: Harriette Gibson, Admin. Sec., ASCRS, 320 W. Lafayette, Detroit, Mi. 48226. (313) 961-7880.

May 4-11—**14th Biennial Western Conference on Anesthesiology.** Princess Kaiulani Hotel, Honolulu. One week. Contact: Murray G. Atnikov, MD, Sec-Treas, BWCA Travel Headquarters, P.O. Box 32366, San Antonio, Tex. 78216.

May 8—**Industrial Back Injuries.** PMC. Thursday.

May 9—**Office Orthopedics.** USC. Friday.

May 15-17—**Neurosurgery.** UCSF and American College of Surgeons at Hilton Hotel, San Francisco. Thursday-Saturday.

May 17—**American College of Surgeons, Northern California**

(Continued on Page 31)

When low back pain*
interferes...
Help relieve pain, restore mobility with
PARAFON FORTE® tablets
chlorzoxazone † 250 mg , acetaminophen 300 mg
*This drug has been evaluated as "probably" effective for this indication.
See brief summary of prescribing information on facing page for Indications, Contraindications, Warnings, Precautions and Adverse Reactions.
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PARAFON FORTE® tablets help relieve pain, restore mobility and stop pain-spasm feedback by providing:

a nonsalicylate analgesic equal to aspirin for relief of pain,[1,2] yet unlikely to cause the gastric irritation,[2,3] allergic reactions[2] or increased bleeding time[4] associated with aspirin therapy...

and a skeletal muscle relaxant shown in extensive clinical studies to afford relief of discomfort in acute musculoskeletal conditions*[5-7] but which is not an antihistamine or tranquilizer derivative and is unlikely to produce a tranquilizing or sedative effect.[5,7,8]

*Indications: Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:

"Probably" effective as an adjunct to rest and physical therapy for the relief of discomfort associated with acute, painful musculoskeletal conditions. The mode of action of this drug has not been clearly identified, but may be related to its sedative properties. Chlorzoxazone does not directly relax tense skeletal muscles in man.

Contraindications: Sensitivity to either component.
Warnings: *Usage in Pregnancy*—Use in women of childbearing potential only when potential benefits outweigh possible risks.
Precautions: Exercise caution in patients with known allergies or history of drug allergies. If a sensitivity reaction or any signs or symptoms suggestive of liver dysfunction are observed, the drug should be stopped.
Adverse Reactions: Occasionally, drowsiness, dizziness, lightheadedness, malaise, overstimulation or gastrointestinal disturbances may be noted; rarely, allergic-type skin rashes, petechiae, ecchymoses, angioneurotic edema or anaphylactic reactions. In rare instances, chlorzoxazone may possibly have been associated with gastrointestinal bleeding. While PARAFLEX® (chlorzoxazone) tablets and other chlorzoxazone-containing products have been suspected as being the cause of hepatic toxicity in approximately twenty-four patients, it was not possible to state that the dysfunction was or was not drug induced.
Usual Adult Dosage: Two tablets q.i.d.
Supplied: Scored, light green tablets, imprinted "McNEIL"—bottles of 100.

References: **1.** Batterman, R.C., and Grossman, A.J.: Fed. Proc. *14*:316, 1955. **2.** Goodman, L.S., and Gilman, A., ed.: The Pharmacological Basis of Therapeutics, ed. 4. New York, The Macmillan Company, 1970. **3.** Vickers, F.N.: Gastroint. Endosc. *14*:94, 1967. **4.** Mielke, C.H., Jr., and Britten, A.F.H.: New Engl. J. Med. *282*:1270, 1970 (Corresp.). **5.** Vernon, W.G.: Curr. Therap. Res. *14*:801, 1972. **6.** Scheiner, J.J.: Curr. Therap. Res. *14*:168, 1972. **7.** Walker, J.M.: Curr. Therap. Res. *15*:248, 1973. **8.** Data on file, McNeil Laboratories, Inc.

†U.S. Patent No. 2,895,877

McNEIL McNeil Laboratories, Inc.
Fort Washington, Pa. 19034

(Continued from Page 29)

Chapter. Hilton Hotel, San Francisco. Saturday. Contact: Dorothy Archbold, Exec. Sec., 2249 Van Ness Ave., No. 2, San Francisco 94109. (415) 221-4810, ext. 251

May 17—**Surgical Anatomy and Surgery of the Chest.** International College of Surgeons, U.S. Section, at Los Angeles Orthopaedic Hospital. Saturday. 8 hrs. $50. Contact: Irving Rehman, PhD, Chr., Postgraduate and Ongoing Education Committee, 5153 Tampa Ave., Tarzana 91356. (213) 344-3305.

May 22-23—**Phaco-Fragmentation.** UCSF. Thursday-Friday.

May 22-23—**Sensory and Perceptual Dysfunction.** USC. Thursday-Friday.

May 25-29—**American College of Emergency Physicians, California Chapter.** See Of Interest To All, May 25-29.

May 31—**Head and Spinal Cord Injuries.** DREW at Martin Luther King Hospital, Los Angeles. Saturday.

June 5-6—**Tendon and Nerve Injuries of the Hand.** PMC. Thursday-Friday.

June 12-13—**Highlights of Modern Ophthalmology.** PMC. Thursday-Friday.

June 12-15—**California Society of Anesthesiologists—Annual Scientific Meeting.** Hyatt Regency, San Francisco. Thursday-Sunday. Contact: Norman Catron, Exec. Sec., CSA, 100 S. Ellsworth Ave., Suite 806, San Mateo 94401. (415) 343-4644.

June 16-20—**Anterior Segment Diseases and Surgery.** USC. Monday-Friday.

June 26-27—**Phaco-Fragmentation.** UCSF. Thursday-Friday.

August 6-10—**Urology—Annual Advanced Seminar.** UCLA at UC Residential Conference Center, Lake Arrowhead. Wednesday-Sunday.

August 17-29—**Temporal Bone Surgical Dissection Course.** Ear Research Institute, Los Angeles. Two weeks. $1200 for otolaryngologists; $900 for residents. Contact: Jack L. Pulec, MD, Ear Research Institute, 2130 W. 3rd St., Los Angeles 90057.

OF INTEREST TO ALL PHYSICIANS

April 14-20—**Introduction to Diving Medicine.** UCSF at VA Hospital, Fresno. Monday-Sunday.

April 15—**Assault or Negligence: Doctor's Choice.** UCSF. Tuesday

April 16-18—**Association of Planned Parenthood Physicians—13th Annual Scientific Meeting and Postgraduate Program.** Century Plaza Hotel, Los Angeles. Wednesday-Friday. Contact: Joseph E. Davis, MD, 810 7th Ave., N.Y. 10019. (212) 541-7800.

April 17-18—**Obesity.** USC. Thursday-Friday.

April 19-20—**Ethical Issues in Modern Medical Practice.** UCLA. Saturday-Sunday.

April 21-25—**Emergency Medicine.** USC at Kona Surf Hotel, Kona, Hawaii. Monday-Friday.

April 21-25—**Family Planning.** See Ob-Gyn, April 21-25.

April 21-May 2—**Emergency Department Medicine in Practice.** UCLA and Harbor General Hospital at Harbor Gen. Hosp., Torrance. Two weeks.

April 25—**Prevention and Indirect Services.** Kings View Foundation at Sheraton Inn, Fresno. Friday. $20. Directed to physicians interested in various aspects of prevention in fields of mental health, developmental disabilities, substance abuse and gerontology. Contact: Kings View Foundation, Public Information Dept., P.O. Box 512, Reedley 93654. (209) 638-3655.

April 25-26—**Human Sexuality and Medicine.** CMA at Ahwahnee Hotel, Yosemite. Friday-Saturday.

April 25-26—**Medical Applications of Behavior Modification to Stroke, Heart Disease, Spinal Injury and Cancer.** PMC. Friday-Saturday. $125.

April 25-27—**Advances in the Control & Management of Chronic Pain.** UCLA. Friday-Sunday.

April 28-May 1—**Aerospace Medical Association—46th Annual Scientific Meeting.** Hilton Hotel, San Francisco. Monday-Thursday. 18 hrs. Contact: Merrill H. Goodwin, MD, Exec. VP, Aerospace Med. Assn., Washington National Airport, Washington, D.C. 20001. (202) 638-2190.

May 2—**The Thyroid.** See Medicine, May 2.

May 9-10—**San Joaquin Valley Counties Postgraduate Institute.** CMA at Ahwahnee Hotel, Yosemite. Friday-Saturday.

May 17—**Clinical Pharmacology Conference — 6th Annual.** STAN at Palo Alto Medical Research Foundation, Palo Alto. Saturday.

May 19-23—**Topics in Emergency Medicine.** UCSF. Monday-Friday.

May 21—**Medical Education at the Crossroads—XVII Annual Medical Staff Symposium.** Memorial Hospital Medical Center, Long Beach. Wednesday. Contact: Margaret Frederick, Exec. Sec., Center for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3823.

May 25-29—**American College of Emergency Physicians, California Chapter—4th Annual Scientific Assembly.** Sheraton-Harbor Island Hotel, San Diego. Sunday-Thursday. 14 hrs. $100, ACEP members registering before April 30; $125, members registering after April 30 and non-members. Contact: ACEP, Calif. Chapter, 23 Altarinda Rd., Suite C, Orinda 94563.

June 4-6—**UCLA School of Medicine Alumni Postgraduate Institute.** Wednesday-Friday.

June 19-21—**Management of Medical Problems in Hospital and Office Practice.** PMC. Thursday-Saturday.

June 22-25—**The Physician as Sex Educator and Counselor.** UCLA at Asilomar Conference Grounds, Pacific Grove. Sunday-Wednesday.

August 11-15—**Postgraduate Refresher Course—18th Annual.** USC at Sheraton-Waikiki Hotel, Honolulu. Monday-Friday.

August 24-29—**Family Practice Refresher Course—3rd Annual.** UCD. Sunday-Friday.

PRECEPTORSHIPS AND TRAINEESHIPS

Training for Physicians in General Internal Medicine. LLU. Four weeks or more, by arrangement. Bedside and classroom training, practical aspects of clinical care and management. 160 hrs. Contact: John E. Peterson, MD, LLU.

Training of Physicians in Modern Concepts of Pulmonary Care. LLU. Four weeks or more, by arrangement. Diagnostic and therapeutic methods in medical chest disease, physiological methodology of modern pulmonary care programs, use of new instrumentation in the field. 160 hrs. Contact: John E. Hodgkin, MD, Chief, Section of Medical Chest Diseases, LLU.

Training for Physicians in Nephrology. LLU. Four weeks or more, by arrangement. Hemodialysis, peritoneal displays, renal biopsy, and kidney transplantation. 160 hrs. Contact: Robert E. Soderblom, MD, LLU.

Preceptorships in Cardiology. PMC. By arrangement. $200 per mo.; $500 for 3 mos. Contact: Arthur Selzer, MD, PMC.

Preceptorships in Practical Office Dermatology. PMC. Wednesdays or Fridays, 9:00 a.m.-12:00 noon, for 10 weeks. Periods begin Oct., Jan., or April. $100. Contact: Harold M. Schneidman, MD, Dept. of Dermatology, PMC.

Preceptorships in Infectious Disease. PMC. Full time for four weeks. To be arranged. $250. Contact: Rodney J. Valentine, MD, Chief, Div. of Infectious Diseases, PMC.

Preceptorships in Basic Sciences, Biochemistry and Biophysics, Dermatology, Echocardiography, International Health, Microbiology, Neurological Surgery, Obstetrics and Gynecology, Pediatrics, Pharmacology and Experimental Therapeutics, Physiology, Psychiatry, Urology. UCSF. By special arrangement.

Traineeships in Renal Dialysis. UCSF. By special arrangement.

AUDIO-DIGEST FOUNDATION

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OREGON

COUNCIL ON MEDICAL EDUCATION

THIS BULLETIN of information regarding continuing education programs and meetings of various medical organizations in Oregon is supplied by the Council on Medical Education of the Oregon Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Council on Medical Education, Oregon Medical Association, 2164 S.W. Park Place, Portland, Oregon 97205; or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

University of Oregon Medical School, Family Practice Center, 3181 S.W. Sam Jackson Park Road, Portland 97201:

Every Thursday, 8:00 a.m. to 9:00 a.m.—**Family Practice Grand Rounds.** Contact: David D. Smith, MD, Department of Family Practice, University of Oregon Medical School.

Providence Hospital, 700 N.E. 47th Ave., Portland 97213 (Contact: Marian Campbell, Department of Medical Education, 503-234-8211):

April 23, Wednesday, 8:00 a.m. (Auditorium, Providence Hall)—**Prophylactic Antibiotics**—D. Gilbert, MD.

May 7, Wednesday, 8:00 a.m. (Auditorium, Providence Hall)—**Providence Oncology Service: Problems and Progress**—G. Doty, MD, P. Kane, MD, D. Regan, MD.

May 21, Wednesday, 8:00 a.m. (Auditorium, Providence Hall)—**Modern Concepts and Treatment of Severe Hypertension**—W. Bennett, MD.

May 28, Wednesday, 8:00 a.m. (Auditorium, Providence Hall)—**Results of the Analysis of Ileo-jejunal Bypass Surgery at Providence Hospital**—R. Gore, MD.

ANESTHESIOLOGY

May 17-19—**Oregon Society of Anesthesiologists, Inc. Annual Meeting.** Salishan, Gleneden Beach, Oregon 97388. Contact: Lynn Husband, MD, 2212 N.W. Pettygrove, Portland 97210.

CARDIOLOGY

June 5-7—**Progress in Coronary Artery Disease and Valvular Heart Disease.** Portland. Contact: S. H. Rahimtoola, University of Oregon Medical School, 3181 S.W. Sam Jackson Park Road, Portland 97201.

FAMILY PRACTICE

Every Thursday, 8:00 a.m. to 9:00 a.m.—**Family Practice Grand Rounds.** Family Practice Center, University of Oregon Medical School, Portland. Contact: David D. Smith, MD Department of Family Practice, University of Oregon Medi

cal School, 3181 S.W. Sam Jackson Park Road, Portland 97201.

May 1-4—**Oregon Academy of Family Practice 28th Annual Scientific Assembly.** Jantzen Beach Thunderbird, Portland. Contact: Ms. Skippie Patterson, Oregon Academy of Family Practice, 2153 S.W. Main, Portland 97205.

INTERNAL MEDICINE

May 15-17—**Oregon Society of Internal Medicine Annual Meeting.** Inn of the Sevnth Mountain, Bend. Contact: Ted Lawson, Oregon Society of Internal Medicine, 2164 S.W. Park Place, Portland 97205.

NEUROLOGY

June 7-8—**Oregon Neurosurgical Society Annual Meeting.** Jantzen Beach Thunderbird, Portland. Contact: Michael Mason, MD, 2525 N.W. Lovejoy, Portland 97210.

OF INTEREST TO ALL PHYSICIANS

May 18-23—**Action and Accountability for Mental Development.** Portland Hilton, Portland. Contact: The American Association on Mental Deficiency, 5201 Connecticut Avenue, N.W., Washington, D.C. 20015 (202) 244-8143.

May 30-31—**Hypertension: The Challenge to the Clinician.** Portland, Jantzen Beach Thunderbird. Sponsored by the University of Oregon Medical School. Contact: M. Roberts Grover, Jr., MD, Associate Dean, University of Oregon Medical School, 3181 SW Sam Jackson Park Road, Portland 97201, (503) 225-8228. Acceptable for 10 hours Category I credit.

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In order to have future activities listed here or to receive information on these and other activities, please write Ms. Joan M. Kelday, Information Specialist, Continuing Medical Education, WAMI Program, University of Washington School of Medicine, E-301, Health Sciences Building, SC-45, Seattle, Washington 98195. Phone: (206) 543-6995.

April 24-25—**Conference on Respiratory Care.** Thursday-Friday. Univ. of Wash. Health Sciences Center, Seattle. Hours not set. $75. Contact: Richard L. Reimer, Asst. D.r. CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

April 28-May 2—**Emergency Medicine Institute.** Monday-Friday. Univ. of Wash. Health Sciences Center, Seattle. 40 hrs. $250. Contact: Richard L. Reimer, Asst. Dir. CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

April 29-30—**Exercise Testing Workshop.** Tuesday-Wednesday. Univ. of Wash. Health Sciences Center, Seattle. 12 hrs. $95. Contact: Richard L. Reimer, Asst. Dir. CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

May 14-16—**Advances in Internal Medicine.** Wednesday-Friday. University Tower Hotel, Seattle. 18 hrs. $150. Contact: Richard L. Reimer, Asst. Dir. CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

May 16-17—**Washington Academy of Family Physicians Annual Meeting.** Friday-Saturday. Inn-at-the-Quay, Vancouver, Wash. 10 AAFP hrs. Contact: Walter Lapsley, Exec. Secretary, WAFP, 10003 SE Evergreen Highway, Vancouver, WA 98664.

May 16-17—**Puget Sound Academy of Otolaryngology Annual Meeting.** Friday-Saturday. Olympic Hotel, Seattle. Contact: Joseph W. Walike, MD, 1118 9th Ave., Seattle 98101. (206) 623-3700.

May 22-23—**Pediatric Care for Family Practitioners.** Thursday-Friday. Children's Orthopedic Hospital and Medical Center, Seattle. 12 hrs. $35. Contact: William O. Robertson, MD, Director of Medical Education, Children's Orthopedic Hospital, P.O. Box 5371, Seattle 98105. (206) 634-5072.

May 25-27—**Alaska State Medical Association Annual Meeting.** Sunday-Tuesday. Glacier Bay, Alaska. Contact: Mrs. Martha L. MacDermaid, Alaska State Medical Assoc., 1135 8th Ave., Anchorage, Alaska 99501.

June 6-7—**Advances in Otolaryngology and Facial Plastic Surgery.** Friday-Saturday. Virginia Mason Medical Center Auditorium, Seattle. 9 hrs. $50. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) MA 3-3700, Ext. 470.

June 12-14—**Montana Academy of Family Practice Annual Meeting.** Thursday-Saturday. Farmont Hot Springs, Gregson, Montana. Contact: Francis Bertaglio, MD, 513 Main St., Deer Lodge, Montana 59722.

June 22-25—**Pacific Northwest OB-GYN Society Annual Meeting.** Sunday-Wednesday. Sun Valley, Idaho. Contact: Ms. Sylvia Gibbons, Exec. Secretary, 1220 Boren Ave., Suite 1105, Seattle 98101. (206) 682-5119.

July 30-August 1—**Idaho Medical Association Annual Meeting.** Wednesday-Friday. The Lodge, Sun Valley, Idaho. Contact: Armand L. Bird, Exec. Director, 407 W. Bannock St., Boise, Idaho 83702.

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Quail Lodge, Carmel

March 21-22, 1975

- Convulsions in Children
- Immunology
- Psychological Development
- Total Joint Replacement
- Pain
- Neonatal Intensive Care
- Hypertension
- Depression

SPECIAL CONFERENCE ON HUMAN SEXUALITY AND MEDICINE

The Ahwahnee, Yosemite

April 25-26, 1975

- Identification and Management of Sexual Problems in Medical Practice
- Female Sexuality
- Today's Lifestyles and Sexually Transmitted Diseases
- Sexual Dysfunction
- Sex and Aging
- Gonorrhea Screening
- Homosexuality

SAN JOAQUIN VALLEY COUNTIES

The Ahwahnee, Yosemite

May 9-10, 1975

- Venereal Disease
- Hepatitis
- Arthritis
- Pulmonary Disease
- Vasectomy
- Neonatal and Pediatric Infection
- Infectious Diarrheas
- Intestinal Parasites

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March 21-22, Carmel
Quail Lodge

☐ **HUMAN SEXUALITY**
April 25-26
The Ahwahnee, Yosemite

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The Ahwahnee, Yosemite

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Sodium	120 milligrams (865 mg/100 gm)

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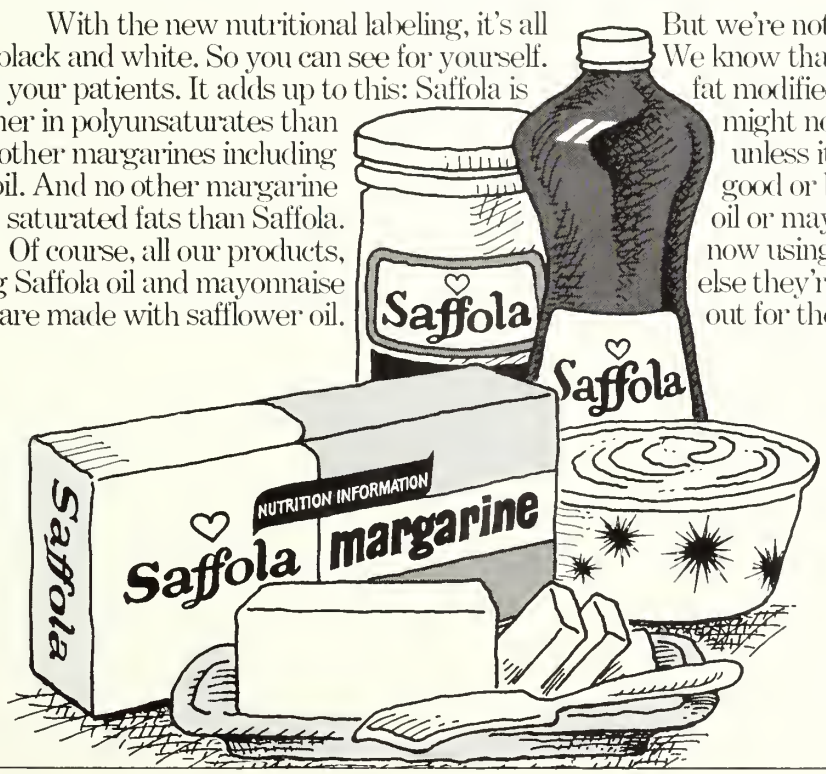

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1. Gertler, M. M., et al.: Geriatrics *25*:134-148 (May) 1970.

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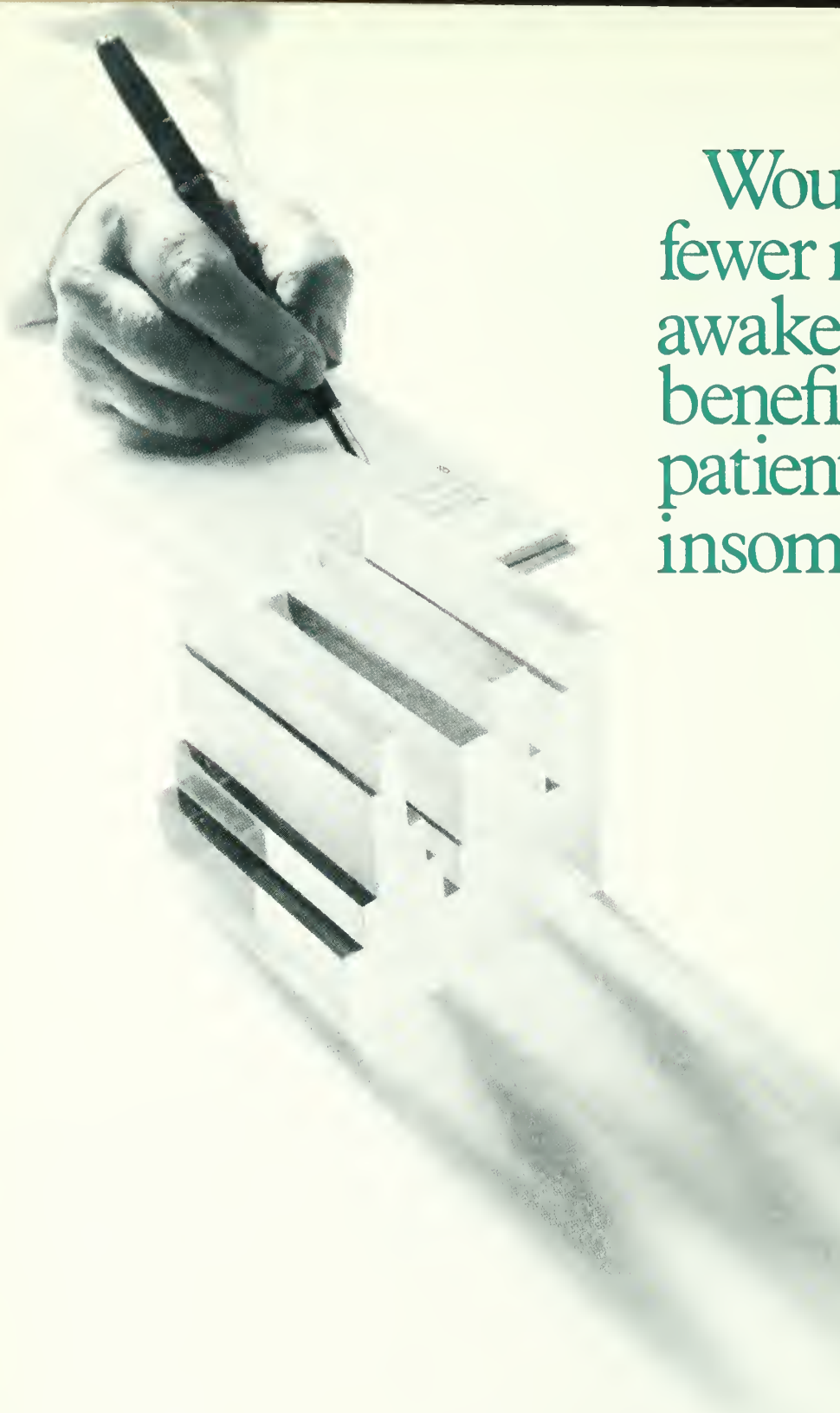

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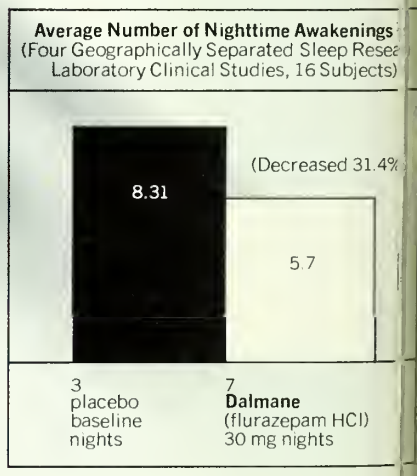

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Precautions: In elderly and debilitated, initial dosage should be limited to 15 mg to preclude oversedation, dizziness and/or ataxia. If combined with other drugs having hypnotic or CNS-depressant effects, consider potential additive effects. Employ usual precautions in patients who are severely depressed, or with latent depression or suicidal tendencies. Periodic blood counts and liver and kidney function tests are advised during repeated therapy. Observe usual precautions in presence of impaired renal or hepatic function.

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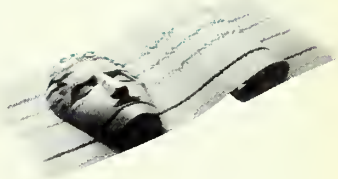

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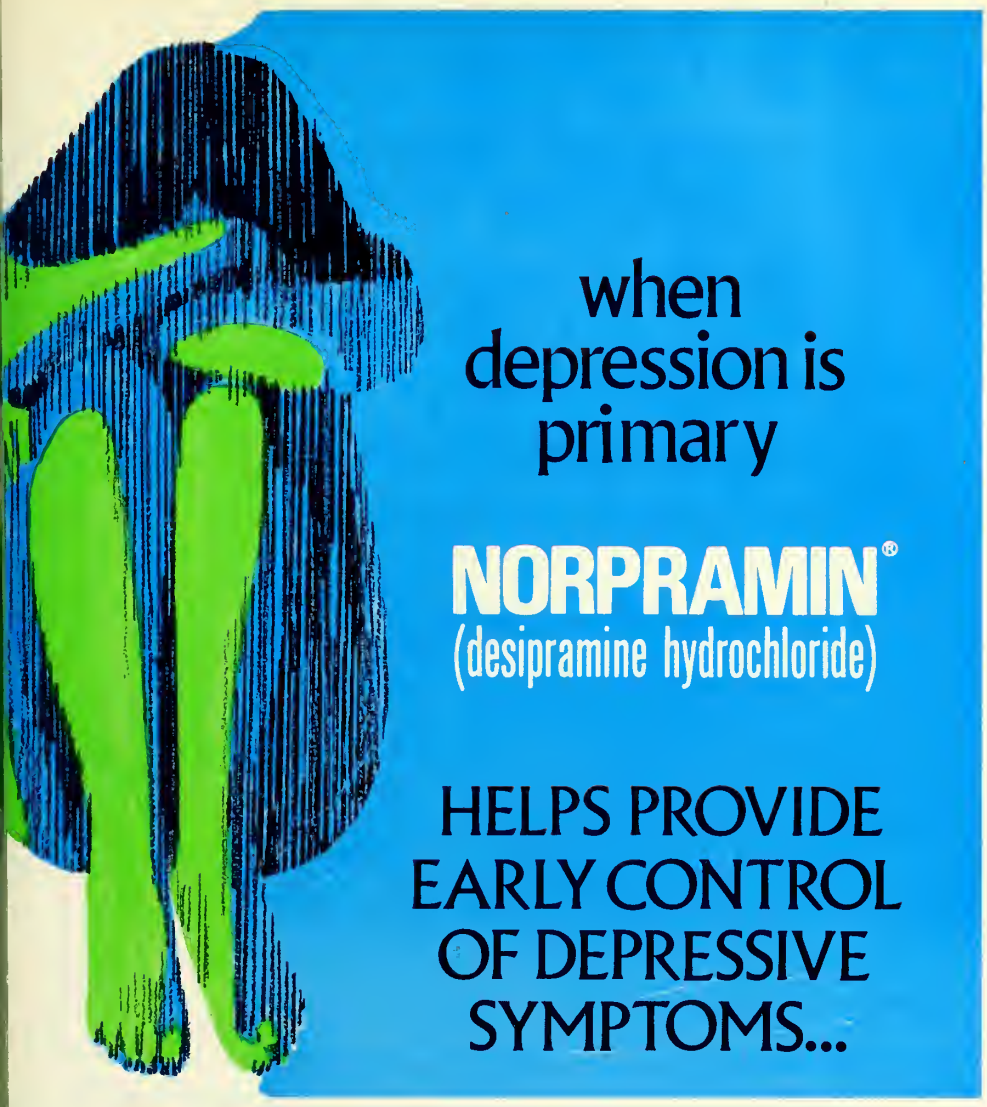
PHARMACEUTICALS INC.
Buffalo, New York 14213

©1974, W. P. Inc.

When you see anxiety-look for depression
NORPRAMIN®
(desipramine hydrochloride)



Anxiety is an invidious symptom. It feeds upon sickness, gnaws, grows and invades every cranny of psychic pathology adding intensity to torment. Anxiety as a symptom secondary to depression may be so dominant that it obscures the primary diagnosis. It may suggest treatment with tranquilizers which often help. But as the vampire of legend had to have a laurel stake driven through its heart to truly die, so anxiety secondary to depression will not cease to nibble and bite until an antidepressant eradicates the primary illness—and symptomatic anxiety starves

Norpramin® (desipramine hydrochloride) 25 mg. and 50 mg. tablets.

IN BRIEF:

Indications: Norpramin® (desipramine hydrochloride) is indicated for the relief of depressive symptoms. Endogenous depressions are more likely to be alleviated than others.

Contreindications: Desipramine hydrochloride should not be given within two weeks of treatment with a monoamine oxidase inhibitor. Contraindications include the acute recovery period following myocardial infarction and hypersensitivity to the drug. Cross sensitivity with other dibenzazepines is a possibility.

Wernings: 1. Extreme caution should be used in patients: (a) with cardiovascular disease, (b) with a history of urinery retention or glaucoma, (c) with thyroid disease or those on thyroid medication, (d) with a history of seizure disorder. 2. This drug is capable of blocking the antihypertensive effect of guanethidine and similarly acting compounds. 3. *Use in Pregnency:* Safe use during pregnancy and lactation has not been established. 4. *Use in Children:* Norpramin® (desipramine hydrochloride) is not recommended for use in children. 5. This drug may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. Therefore, the patient should be cautioned accordingly.

Precautions: This drug should be dispensed in the least possible quantities to depressed outpatients, since suicide has been accomplished with drugs of this class. If possible, dispense in child-resistant containers. It should be kept out of reach of children. Reduce dosage, or alter treatment, if serious adverse effects occur. Norpramin® (desipramine hydrochloride) therepy in patients with manic-depressive illness may induce a hypomanic state after the depressive phase terminates and may cause exacerbation of phychosis in schizophrenic patients. Use cautiously with anticholinergic or sympathomimetic drugs. Response to alcoholic beverages may be exaggerated. In the concurrent administration of ECT and antidepressant drugs one should consider the possibility of increased risk relative to benefits. Discontinue as soon es possible prior to elective surgery because of possible cardiovascular effects. Hypertensive episodes have been observed during surgery in patients on desipramine hydrochloride. Leukocyte and differential counts should be performed in any patient who develops fever and sore throat during therapy; the drug should be discontinued if there is neutropenia.

Adverse Reactions: *Cardiovascular:* hypotension, hypertension, tachycardia, palpitation, arrhythmias, heart block, myocardial infarction, stroke. *Psychiatric:* confusional states (especially in the elderly), hallucinations, disorientation, delusions; anxiety, agitation; insomnia and nightmares; hypomanie; exacerbation of phychosis. *Neurological:* paresthesias of extremities; incoordination, ataxia, tremors, peripheral neuropathy; extrapyramidal symptoms; seizures; alteration in EEG patterns; tinnitus. *Anticholinergic:* dry mouth, and rarely associated sublingual adenitis; blurred vision, disturbance of accommodation, mydriasis; constipation, paralytic ileus; urinary retention, delayed micturition, hypotonic bladder. *Allergic:* skin rash, petechiae, urticaria, itching, photosensitization, edema (of face and tongue or general), drug fever. *Hemetologic:* agranulocytosis, eosinophilia, purpura, thrombocytopenia. *Gastrointestinal:* anorexia, nausea and vomiting, epigastric distress, peculiar taste, abdominal cramps, diarrhea, stomatitis, black tongue. *Endocrine:* gynecomastia; breast enlargement and galactorrhea in the female; increased or decreased libido, impotence, testicular swelling; elevation or depression of blood sugar levels. *Other:* Jaundice (simulating obstructive), altered liver function; weight gain or loss; perspiration, flushing; urinary frequency, nocturia; parotid swelling; drowsiness, dizziness, weakness and fatigue, headache; alopecia. *Withdrawal Symptoms:* Though not indicative of eddiction, abrupt cessation efter prolonged therapy may produce nausea, headache and malaise.

Dosage and Administration: *The usual adult dose:* 50 mg. three times daily; increase if necessary after 7 to 10 days to maximum of 200 mg. daily. Dosages above 200 mg. per day are not recommended. *Maintenance:* At a lower dose adequate to maintain remission. *Adolescent and geriatric petient dose:* 25 to 50 mg. daily if necessary.

Overdosege: There is no specific antidote for desipramine, nor are there specific phenomena of diagnostic velue characterizing poisoning by the drug. The principles of management of coma and shock by means of the mechanical respirator, cardiac pacemaker, monitoring of central venous pressure and regulation of fluid- and acid-base belance are well known in most medicel centers. If heart failure is imminent, digitalize promptly.

LAKESIDE LABORATORIES
Division of Richardson-Merrell Inc
Milwaukee, Wisconsin 53201

Convenient B.I.D. Gantanol®
(sulfamethoxazole)

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Acute, recurrent or chronic nonobstructed urinary tract infections (primarily pyelonephritis, pyelitis and cystitis) due to susceptible organisms. ***Note:* Carefully coordinate *in vitro* sulfonamide sensitivity tests with bacteriologic and clinical response; add aminobenzoic acid to follow-up culture media. The increasing frequency of resistant organisms limits the usefulness of antibacterials including sulfonamides, especially in chronic or recurrent urinary tract infections.** Measure sulfonamide blood levels as variations may occur; 20 mg/100 ml should be maximum total level.

Contraindications: Sulfonamide hypersensitivity; pregnancy at term and during nursing period; infants less than two months of age.

Warnings: Safety during pregnancy has not been established. Sulfonamides should not be used for group A beta-hemolytic streptococcal infections and will not eradicate or prevent sequelae (rheumatic fever, glomerulonephritis) of such infections. Deaths from hypersensitivity reactions, agranulocytosis, aplastic anemia and other blood dyscrasias have been reported and early clinical signs (sore throat, fever, pallor, purpura or jaundice) may indicate serious blood disorders. Frequent CBC and urinalysis with microscopic examination are recommended during sulfonamide therapy. Insufficient data on children under six with chronic renal disease.

Precautions: Use cautiously in patients with impaired renal or hepatic function, severe allergy, bronchial asthma; in glucose-6-phosphate dehydrogenase-deficient individuals in whom dose-related hemolysis may occur. Maintain adequate fluid intake to prevent crystalluria and stone formation.

Adverse Reactions: *Blood dyscrasias* (agranulocytosis, aplastic anemia, thrombocytopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia); *allergic reactions* (erythema multiforme, skin eruptions, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis); *gastrointestinal reactions* (nausea, emesis, abdominal pains, hepatitis, diarrhea, anorexia, pancreatitis and stomatitis); *CNS reactions* (headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo and insomnia); *miscellaneous reactions* (drug fever, chills, toxic nephrosis with oliguria and anuria, periarteritis nodosa and L.E. phenomenon). Due to certain chemical similarities with some goitrogens, diuretics (acetazolamide, thiazides) and oral hypoglycemic agents, sulfonamides have caused rare instances of goiter production, diuresis and hypoglycemia as well as thyroid malignancies in rats following long-term administration. Cross-sensitivity with these agents may exist.

Dosage: *Systemic sulfonamides are contraindicated in infants under 2 months of age* (except adjunctively with pyrimethamine in congenital toxoplasmosis).

Usual adult dosage: 2 Gm (4 tabs or teasp.) initially, then 1 Gm *b.i.d.* or *t.i.d.* depending on severity of infection.

Usual child's dosage: 0.5 Gm (1 tab or teasp.)/20 lbs of body weight initially, then 0.25 Gm/20 lbs *b.i.d.* Maximum dose should not exceed 75 mg/kg/24 hrs.

Supplied: Tablets, 0.5 Gm sulfamethoxazole; Suspension, 0.5 Gm sulfamethoxazole/teaspoonful.

ROCHE

Roche Laboratories
Division of Hoffmann-La Roche Inc.
Nutley, New Jersey 07110

Bacterial proliferation in the urine is a function of time and retention, as the chart below indicates. Because each 1-Gm dose provides up to 12 hours' antibacterial activity, Gantanol protects the patient during the hours of sleep, when urinary retention favors bacterial buildup in the bladder. Counts of susceptible *E. coli* are usually reduced from 10^5/ml to sterile urine within 48 hours.

your patient sleeps

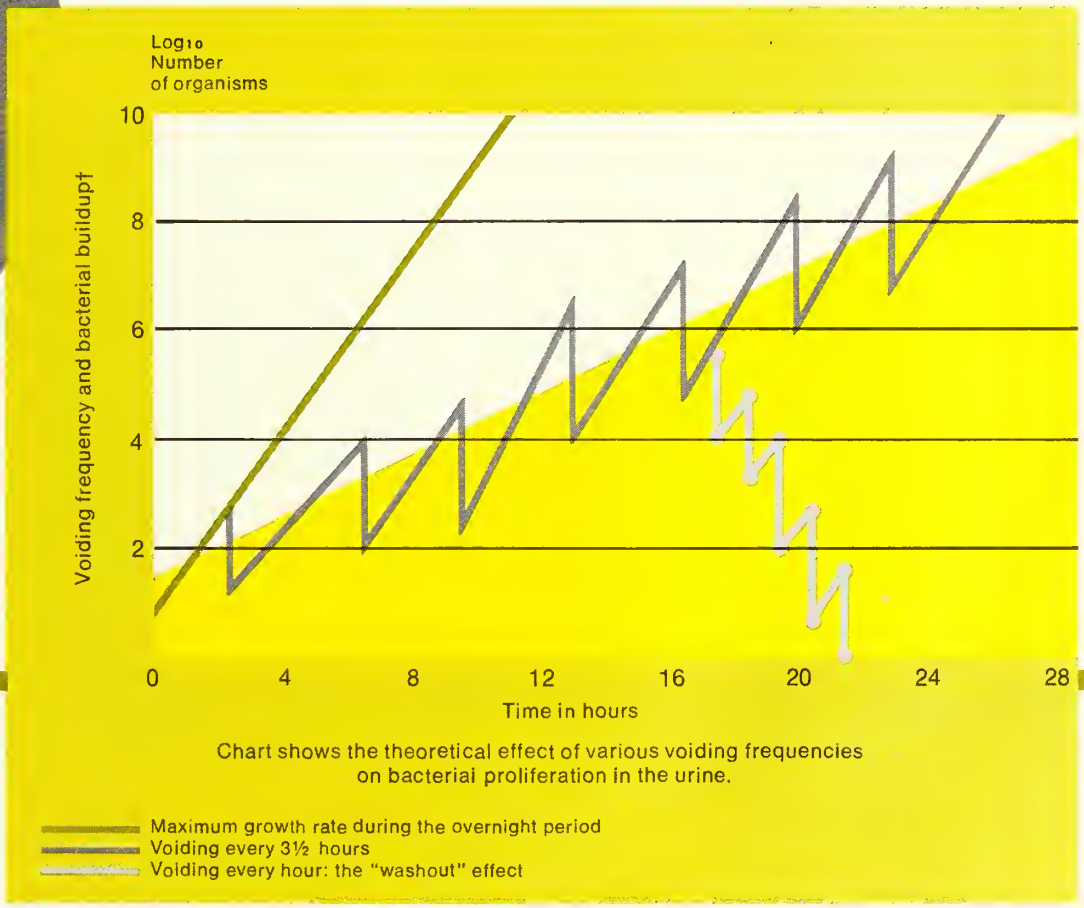


Chart shows the theoretical effect of various voiding frequencies on bacterial proliferation in the urine.

†Adapted from O'Grady F, Cattell WR: *Brit J Urol 38*:156, 1966

For acute nonobstructed cystitis*

Gantanol® B.I.D.
sulfamethoxazole/Roche®

Basic therapy with convenience:

4 tablets (0.5 Gm each) STAT — then 2 tablets B.I.D. for 10-14 days

*due to susceptible organisms

Before prescribing, see complete prescribing information in SK&F literature or *PDR*. The following is a brief summary.

WARNING
This fixed combination drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual patient. If the fixed combination represents the dosage so determined, its use may be more convenient in patient management. The treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Indications: This combination drug finds its usefulness primarily in the treatment of edema. Any usefulness of triamterene when used with a thiazide in hypertension will derive from its potassium-sparing effect. Either its main diuretic effect or potassium-sparing effect when used with a thiazide drug should be determined by individual titration. (See box warning.)

Edema associated with congestive heart failure, cirrhosis of the liver, the nephrotic syndrome; steroid-induced and idiopathic edema; edema resistant to other diuretic therapy. Also, mild to moderate hypertension.

Contraindications: Pre-existing elevated serum potassium. Hypersensitivity to either component. Continued use in progressive renal or hepatic dysfunction or developing hyperkalemia.

Warnings: **Do not use dietary potassium supplements or potassium salts unless hypokalemia develops or dietary potassium intake is markedly impaired.** Enteric-coated potassium salts may cause small bowel stenosis with or without ulceration. Hyperkalemia (5.4 mEq/L) has been reported in 4% of patients under 60 years, in 12% of patients over 60 years, and in less than 8% of patients overall. Rarely, cases have been associated with cardiac irregularities. Accordingly, **check serum potassium during therapy, particularly in patients with suspected or confirmed renal insufficiency (e.g., elderly or diabetics). If hyperkalemia develops, substitute a thiazide alone. If spironolactone is used comcomitantly with 'Dyazide', check serum potassium frequently**—both can cause potassium retention and sometimes hyperkalemia. Two deaths have been reported in patients on such combined therapy (in one, recommended dosage was exceeded; in the other, serum electrolytes were not properly monitored). Observe patients on 'Dyazide' regularly for possible blood dyscrasias, liver damage or other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving Dyrenium (triamterene, SK&F). Rarely, leukopenia, thrombocytopenia, agranulocytosis, and aplastic anemia have been reported with the thiazides. Watch for signs of impending coma in acutely ill cirrhotics. Thiazides are reported to cross the placental barrier and appear in breast milk. This may result in fetal or neonatal hyperbilirubinemia, thrombocytopenia, altered carbohydrate metabolism and possibly other adverse reactions that have occurred in the adult. When used during pregnancy or in women who might bear children, weigh potential benefits against possible hazards to fetus.

Precautions: Do periodic serum electrolyte and BUN determinations. Do periodic hematologic studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in post-sympathectomy patients. The following may occur: hyperuricemia and gout, reversible nitrogen retention, decreasing alkali reserve with possible metabolic acidosis, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), digitalis intoxication (in hypokalemia). Use cautiously in surgical patients. Concomitant use with antihypertensive agents may result in an additive hypotensive effect. 'Dyazide' interferes with fluorescent measurement of quinidine.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis; rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting (may indicate electrolyte imbalance), diarrhea, constipation, other gastrointestinal disturbances. Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and, rarely, allergic pneumonitis have occurred with thiazides alone.

Supplied: Bottles of 100 capsules; in Single Unit Packages of 100 (intended for institutional use only).

SK&F CO.
Carolina, P.R. 00630
Subsidiary of
SmithKline Corporation

KEEP THE HYPERTENSIVE PATIENT ON THERAPY KEEP THERAPY SIMPLE WITH

DYAZIDE®

Trademark

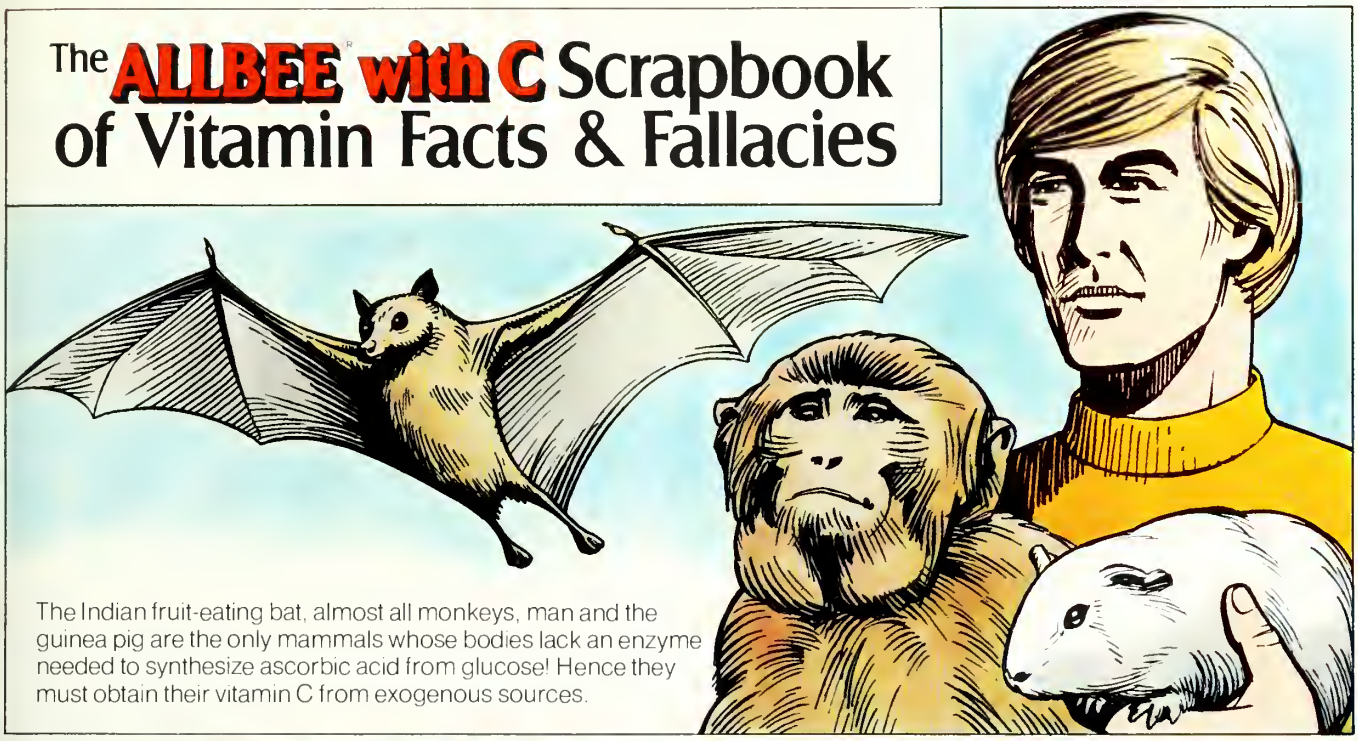
Each capsule contains 50 mg. of Dyrenium® (brand of triamterene) and 25 mg. of hydrochlorothiazide.

Neither inconvenient potassium supplements nor special K^+ rich diets needed as a rule. Just 'Dyazide' once or twice daily for maintenance.

Two prime reasons patients drop out of hypertensive therapy are (1) the patient failed to understand directions, and (2) the regimen was overly complicated. Dosage is simple with 'Dyazide', easily understood, once or twice daily, depending on response. There's no need to complicate the regimen with potassium supplements or unwieldy potassium-rich diets.

TO KEEP BLOOD PRESSURE DOWN AND KEEP POTASSIUM LEVELS UP

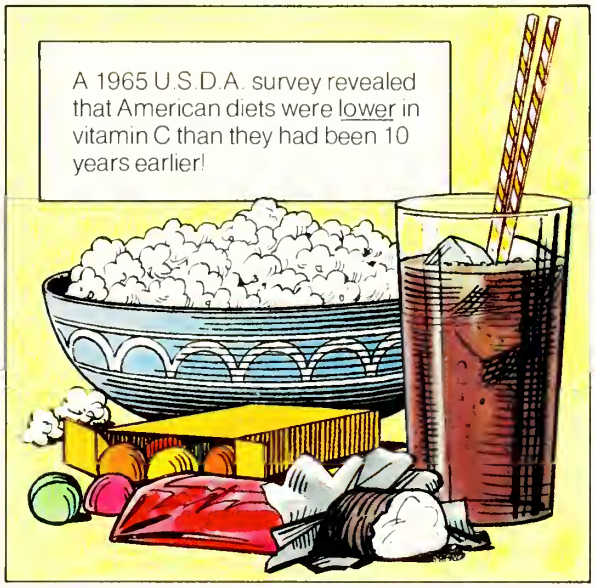
The ALLBEE® with C Scrapbook of Vitamin Facts & Fallacies



The Indian fruit-eating bat, almost all monkeys, man and the guinea pig are the only mammals whose bodies lack an enzyme needed to synthesize ascorbic acid from glucose! Hence they must obtain their vitamin C from exogenous sources.

De Joinville writing about a 13th century crusade reported that barber surgeons had to "cut away the dead flesh from the gums to enable people to masticate their food" The disease he described was probably scurvy.

A 1965 U.S.D.A. survey revealed that American diets were lower in vitamin C than they had been 10 years earlier!

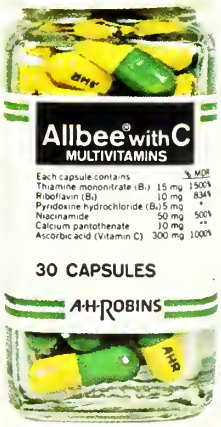


The outer leaves of cabbage and brussels sprouts contain more vitamin C than the heads. Yet, ironically, these are often trimmed away by the grocer to improve appearance and enhance sales appeal! Many housewives trim them even more before cooking!

Available on your prescription or recommendation

ALLBEE® with C

High Potency B-Complex and Vitamin C Formula



A.H. Robins Company, Richmond, Va. 23220 A·H·ROBINS

Spasm reactor?

Donnatal®!

	each tablet, capsule or 5 cc. teaspoonful of elixir (23% alcohol)	each Donnatal No. 2	each Extentab
hyoscyamine sulfate	0.1037 mg.	0.1037 mg.	0.3111 mg
atropine sulfate	0.0194 mg.	0.0194 mg.	0.0582 mg
hyoscine hydrobromide	0.0065 mg	0.0065 mg.	0.0195 mg.
phenobarbital	(¼ gr.) 16.2 mg	(½ gr.) 32.4 mg	(¾ gr.) 48.6 mg.
(warning: may be habit forming)			

Brief summary. Adverse Reactions: Blurring of vision, dry mouth, difficult urination, and flushing or dryness of the skin may occur on higher dosage levels, rarely on usual dosage. Contraindications: Glaucoma; renal or hepatic disease; obstructive uropathy (for example, bladder neck obstruction due to prostatic hypertrophy); or hypersensitivity to any of the ingredients.

A·H·ROBINS A. H. Robins Company Richmond Virginia 23220

Sutter Publications, Inc.

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A Subsidiary of California Medical Association

Relative Value Studies

of the

CALIFORNIA MEDICAL ASSOCIATION

5th Edition, Revised in 1974

Available May 1, 1975 for implementation on or after October 1, 1975

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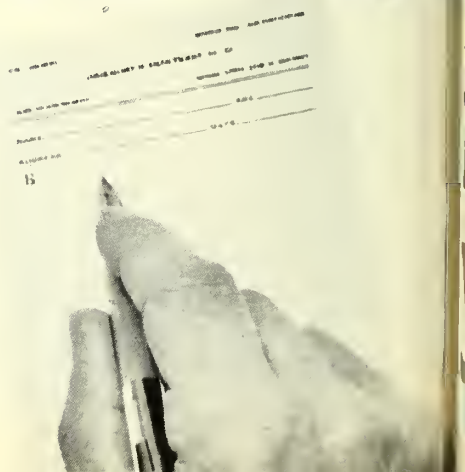
Bioequivalenc



the weight of scientific opinion:

If the pharmacist substituted a chemically equivalent drug for the one you have specified for your patient—could you be certain of that product's safety and effectiveness simply because the chemical content was the same?

Definitely not, unless bioequivalence tests and other quality assurance checks had been conducted. The pharmaceutical industry and many scientists have maintained this position for years, but others have questioned it. Now the Office of Technology Assessment of the Congress of the United States has reported on the issue in its Drug Bioequivalence Study.*

Here are a few definitive statements in the O.T.A. report:

"...the problem of bioinequivalency in chemically equivalent products is a real one. Since the studies in which lack of bioequivalence was demonstrated involved marketed products that met current compendial standards, these documented instances constitute unequivocal evidence that neither the present standards for testing the finished product nor the specifications for materials, manufacturing process, and controls are adequate to ensure that ostensibly equivalent drug products are, in fact, equivalent in bioavailability.

"While these therapeutic failures resulting from problems of bioavailability were recognized and well documented, it is entirely possible that other therapeutic failures and/or instances of toxicity that had a similar basis have escaped attention."

The Pharmaceutical Manufacturers Association supports federal legislative amendments that would require manufacturers of duplicate prescription pharmaceutical products, subject to new drug procedures, to document:

(a) chemical equivalence; and (b) biological equivalence, where bioavailability test methods have been validated as a reliable means of assuring clinical equivalence; or (c) where such validation is not possible, therapeutic equivalence.

In addition, the PMA supports federal legislation that would require certification of all manufacturers of prescription products before they could start in business, annual inspections and certification thereafter, and strict adherence to FDA regulations on good manufacturing practices.

The overall quality of the United States drug supply is excellent. But only a total quality assurance program, envisaged in these and other policy positions adopted by the PMA Board of Directors in 1974, can bring about acceptable levels of performance by all prescription drug manufacturers and thereby assure the integrity of your prescription...

P·M·A

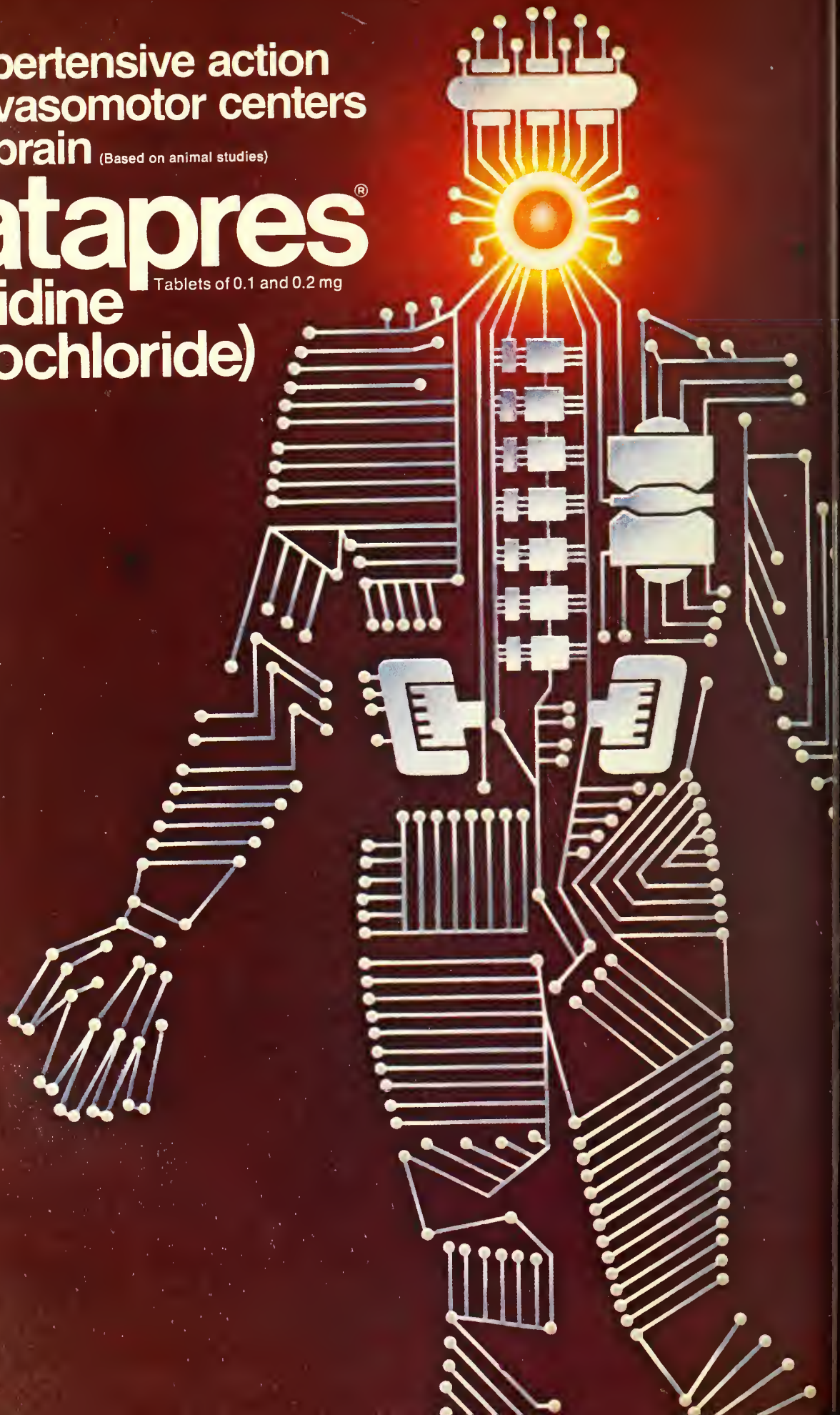
Pharmaceutical Manufacturers Association
1155 Fifteenth Street, N.W.
Washington, D.C. 20005

*Copies of the complete report on Drug Bioequivalence may be obtained from the Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402.

protecting the integrity of your prescription

Now...
antihypertensive action
at the vasomotor centers
in the brain (Based on animal studies)

Catapres®
(clonidine
hydrochloride)
Tablets of 0.1 and 0.2 mg



Central action

Catapres appears to lower blood pressure through central alpha-adrenergic stimulation, as shown in animal studies. This results in diminution—but not blocking—of sympathetic outflow from cardioaccelerator and vasoconstrictor centers in the medulla.

Not a "depleter", "blocker", "inhibitor" or "false transmitter".

Not a rauwolfia

Effective in hypertension, mild to severe

Mild and infrequent orthostatic hypotension

Normal hemodynamic responses to exercise are unaffected

Renal blood flow and glomerular filtration rate essentially unchanged

Mild to moderate potency

The most common side effects are dry mouth, drowsiness and sedation. These generally tend to diminish with continued therapy. Other potential adverse reactions are listed in the Brief Summary.

Catapres® (clonidine hydrochloride)
Tablets of 0.1 mg and 0.2 mg

Indication: The drug is indicated in the treatment of hypertension. As an antihypertensive drug, Catapres (clonidine hydrochloride) is mild to moderate in potency. It may be employed in a general treatment program with a diuretic and/or other antihypertensive agents as needed for proper patient response.

Warnings: Tolerance may develop in some patients necessitating a reevaluation of therapy.
Usage in Pregnancy: In view of embryotoxic findings in animals, and since information on possible adverse effects in pregnant women is limited to uncontrolled clinical data, the drug is not recommended in women who are or may become pregnant unless the potential benefits outweigh the potential risk to mother and fetus.
Usage in Children: No clinical experience is available with the use of Catapres (clonidine hydrochloride) in children.

Precautions: When discontinuing Catapres (clonidine hydrochloride), reduce the dose gradually over 2 to 4 days to avoid a possible rapid rise in blood pressure and associated subjective symptoms such as nervousness, agitation, and headache. Patients should be instructed not to discontinue therapy without consulting their physician. Rare instances of hypertensive encephalopathy and death have been recorded after cessation of clonidine hydrochloride therapy. A causal relationship has not been established in these cases. It has been demonstrated that an excessive rise in blood pressure, should it occur, can be reversed by resumption of clonidine hydrochloride therapy or by intravenous phentolamine. Patients who engage in potentially hazardous activities, such as operating machinery or driving should be advised of the sedative effect. This drug may enhance the CNS-depressive effects of alcohol, barbiturates and other sedatives. Like any other agent lowering blood pressure, clonidine hydrochloride should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease or chronic renal failure.

As an integral part of their overall long-term care, patients treated with Catapres (clonidine hydrochloride) should receive periodic eye examinations. While, except for some dryness of the eyes, no drug-related abnormal ophthalmologic findings have been recorded with Catapres, in several studies the drug produced a dose-dependent increase in the incidence and severity of spontaneously occurring retinal degeneration in albino rats treated for 6 months or longer.

Adverse Reactions: The most common reactions are dry mouth, drowsiness and sedation. Constipation, dizziness, headache, and fatigue have been reported. Generally these effects tend to diminish with continued therapy. The following reactions have been associated with the drug, some of them rarely. (In some instances an exact causal relationship has not been established). These include: Anorexia, malaise, nausea, vomiting, parotid pain, mild transient abnormalities in liver function tests; one report of possible drug-induced hepatitis without icterus and hyperbilirubinemia in a patient receiving clonidine hydrochloride, chlorthalidone and papaverine hydrochloride.

Weight gain, transient elevation of blood glucose, or serum creatine phosphokinase; congestive heart failure, Raynaud's phenomenon; vivid dreams or nightmares, insomnia, other behavioral changes, nervousness, restlessness, anxiety and mental depression. Also rash, angioneurotic edema, hives, urticaria, thinning of the hair, pruritus not associated with a rash, impotence, urinary retention, increased sensitivity to alcohol, dryness, itching or burning of the eyes, dryness of the nasal mucosa, pallor, gynecomastia, weakly positive Coombs' test, asymptomatic electrocardiographic abnormalities manifested as Wenckebach period or ventricular trigeminy.

Overdosage: Profound hypotension, weakness, somnolence, diminished or absent reflexes and vomiting followed the accidental ingestion of Catapres (clonidine hydrochloride) by several children from 19 months to 5 years of age. Gastric lavage and administration of an analeptic and vasopressor led to complete recovery within 24 hours. Tolazoline in intravenous doses of 10 mg at 30-minute intervals usually abolishes all effects of Catapres (clonidine hydrochloride) overdosage.

How Supplied: Catapres, brand of clonidine hydrochloride, is available as 0.1 mg (tan) and 0.2 mg (orange) oval, single-scored tablets in bottles of 100.

For complete details, please see full prescribing information.

Under license from
Boehringer Ingelheim GmbH

BOEHRINGER INGELHEIM

Boehringer Ingelheim

Boehringer Ingelheim Ltd.
Elmsford, New York 10523

to help treat what you often find:
obvious moderate to severe anxiety
with a less obvious underlying depression

TRIAVIL®

containing perphenazine and amitriptyline HCl

a tranquilizer–antidepressant

"...and she'd jump every time the phone rang."

"All right, I agree, she was obviously very anxious...you said she hadn't been sleeping...."

"She felt *tired enough* to sleep... not relaxed enough...food, too... she's too nervous to eat...says she *can't* relax...afraid there's something very wrong with her."

"...that's a good place to start Did you find anything wrong with her?"

Treatment with TRIAVIL—a balanced view.

Tablets TRIAVIL are available in four different combinations affording flexibility and individualized dosage adjustment. Close supervision of patients is essential until satisfactory remission has taken place. Since suicide is a possibility in any depressive illness, patients should not have easy access to large quantities of the drug. The drug may impair alertness and potentiate the response to alcohol. It should not be used during the acute recovery phase following myocardial infarction or given to patients who have received an MAOI within two weeks. TRIAVIL should be used with caution in glaucoma and in patients prone to urinary retention. It is contraindicated in CNS depression and in the presence of evidence of bone marrow depression.

MSD MERCK SHARP DOHME

For a brief summary of prescribing information, please turn to the following page.

'lot a thing... negative... nothing rganically wrong. Still has a air list of somatic complaints. ve tried to reassure her... to let er talk... to help her sort things ut. She's been in to see me a umber of times."

"...what about medication?"

"Just what I was coming to... I've had her on tranquilizers. And *that's* what puzzles me. I'm not getting the response I hoped for. She's no better... perhaps a little worse. It's sad to see."

"...I think *'sad'* may be what you're not seeing! You know, this sounds like another case where the *anxiety* is so clear and pervasive we tend to overlook the depressive part of the picture. I'm not sure that we shouldn't almost always think of anxiety *with* depression... not anxiety alone. Take another look at your records... talk to her some more. If you decide she's depressed, I think you might want to consider TRIAVIL.... It can help relieve her entire symptom complex... control the anxiety... while at the same time treat the depression."

TRIAVIL®

to help treat what you often find: obvious moderate to severe anxiety with a less obvious underlying depression

containing perphenazine and amitriptyline HCl

a tranquilizer–antidepressant

Available:
TRIAVIL® 2-25 Each tablet contains
2 mg perphenazine and 25 mg amitriptyline HCl

TRIAVIL® 2-10 Each tablet contains
2 mg perphenazine and 10 mg amitriptyline HCl

TRIAVIL® 4-25 Each tablet contains
4 mg perphenazine and 25 mg amitriptyline HCl

TRIAVIL® 4-10 Each tablet contains
4 mg perphenazine and 10 mg amitriptyline HCl

INITIAL THERAPY FOR MANY PATIENTS
TRIAVIL® 2-25 (or TRIAVIL® 4-25) t.i.d. or q.i.d.

FOR FLEXIBILITY IN ADJUSTING MAINTENANCE THERAPY
TRIAVIL® 2-10 (or TRIAVIL® 4-10)

CONTRAINDICATIONS: Central nervous system depression from drugs (barbiturates, alcohol, narcotics, analgesics, antihistamines); bone marrow depression; known hypersensitivity to phenothiazines or amitriptyline. Do not give concomitantly with MAOI drugs because hyperpyretic crises, severe convulsions, and deaths have occurred from such combinations. Allow minimum of 14 days between therapies, then initiate therapy with TRIAVIL cautiously, with gradual increase in dosage until optimum response is achieved. Not recommended for use during acute recovery phase following myocardial infarction.

WARNINGS: TRIAVIL should not be given with guanethidine or similarly acting compounds. Use cautiously in patients with history of urinary retention, angle-closure glaucoma, increased intraocular pressure, or convulsive disorders. In patients with angle-closure glaucoma, even average doses may precipitate an attack. Patients with cardiovascular disorders should be watched closely. Tricyclic antidepressants, including amitriptyline HCl, particularly in high doses, have been reported to produce arrhythmias, sinus tachycardia, and prolongation of conduction time. Myocardial infarction and stroke have been reported with tricyclic antidepressant drugs. Close supervision is required for hyperthyroid patients or those receiving thyroid medication. Caution patients performing hazardous tasks, such as operating machinery or driving motor vehicles, that drug may impair mental and/or physical abilities. Not recommended in children or during pregnancy.

PRECAUTIONS: Suicide is a possibility in depressed patients and may remain until significant remission occurs. Such patients should not have access to large quantities of this drug.

Perphenazine: Should not be used indiscriminately. Use with caution in patients who have previously exhibited severe adverse reactions to other phenothiazines. Likelihood of untoward actions is greater with high doses. Closely supervise with any dosage. The antiemetic effect of perphenazine may obscure signs of toxicity due to overdosage of other drugs or make more difficult the diagnosis of disorders such as brain tumor or intestinal obstruction. A significant, not otherwise explained, rise in body temperature may suggest individual intolerance to perphenazine, in which case discontinue.

If hypotension develops, epinephrine should not be employed, as its action is blocked and partially reversed by perphenazine. Phenothiazines may potentiate the action of central nervous system depressants (opiates, analgesics, antihistamines, barbiturates, alcohol) and atropine. In concurrent therapy with any of these, TRIAVIL should be given in reduced dosage. May also potentiate the action of heat and phosphorous insecticides.

Amitriptyline: In manic-depressive psychosis, depressed patients may experience a shift toward the manic phase if they are treated with an antidepressant. Patients with paranoid symptomatology may have an exaggeration of such symptoms. The tranquilizing effect of TRIAVIL seems to reduce the likelihood of this effect. When amitriptyline HCl is given with anticholinergic agents or sympathomimetic drugs, including epinephrine combined with local anesthetics, close supervision and careful adjustment of dosages are required.

Caution is advised if patients receive large doses of ethchlorvynol concurrently. Transient delirium has been reported in patients who were treated with 1 g of ethchlorvynol and 75-150 mg of amitriptyline HCl.

Amitriptyline HCl may enhance the response to alcohol and the effects of barbiturates and other CNS depressants.

Concurrent administration of amitriptyline HCl and electroshock therapy may increase the hazards associated with such therapy. Such treatment should be limited to patients for whom it is essential. Discontinue several days before elective surgery if possible. Elevation and lowering of blood sugar levels have both been reported

ADVERSE REACTIONS: Similar to those reported with either constituent alone.

Perphenazine: Side effects may be any of those reported with phenothiazine drugs: extrapyramidal symptoms (opisthotonus, oculogyric crisis, hyperreflexia, dystonia, akathisia, acute dyskinesia, ataxia, parkinsonism) can usually be controlled by the concomitant use of effective antiparkinsonian drugs and/or by reduction in dosage, but sometimes persist after discontinuation of the phenothiazine.

Tardive dyskinesia may appear in some patients on long-term therapy or may occur after drug therapy with phenothiazines and related agents has been discontinued. The risk appears to be greater in elderly patients on high-dose therapy, especially females. Symptoms are persistent and in some patients appear to be irreversible. The syndrome is characterized by rhythmical involuntary movements of the tongue, face, mouth, or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Involuntary movements of the extremities sometimes occur. There is no known treatment for tardive dyskinesia; antiparkinsonism agents usually do not alleviate the symptoms. It is advised that all antipsychotic agents be discontinued if the above symptoms appear. If treatment is reinstituted, or dosage of the particular drug increased, or another drug substituted, the syndrome may be masked. It has been suggested that fine vermicular movements of the tongue may be an early sign of the syndrome, and that the full-blown syndrome may not develop if medication is stopped when lingual vermiculation appears.

Other side effects are skin disorders (photosensitivity, itching, erythema, urticaria, eczema, up to exfoliative dermatitis); other allergic reactions (asthma, laryngeal edema, angioneurotic edema, anaphylactoid reactions); peripheral edema; reversed epinephrine effect; hyperglycemia; endocrine disturbances (lactation, galactorrhea, gynecomastia, disturbances of menstrual cycle); altered cerebrospinal fluid proteins; paradoxical excitement; hypertension, hypotension, tachycardia, and ECG abnormalities (quinidine-like effect); reactivation of psychotic processes; catatonic-like states; autonomic reactions, such as dry mouth or salivation, headache, anorexia, nausea, vomiting, constipation, obstipation, urinary frequency or incontinence, blurred vision, nasal congestion, and a change in pulse rate; hypnotic effects; pigmentary retinopathy; corneal and lenticular pigmentation; occasional lassitude, muscle weakness, mild insomnia. Other adverse reactions reported with various phenothiazine compounds include blood dyscrasias (pancytopenia, thrombocytopenic purpura, leukopenia, agranulocytosis, eosinophilia); liver damage (jaundice, biliary stasis); grand mal convulsions; cerebral edema; polyphagia; photophobia; skin pigmentation; and failure of ejaculation.

Amitriptyline: Note: Listing includes a few reactions not reported for this drug, but which have occurred with other pharmacologically similar tricyclic antidepressant drugs. *Cardiovascular:* Hypotension; hypertension; tachycardia; palpitation; myocardial infarction; arrhythmias; heart block; stroke. *CNS and Neuromuscular:* Confusional states; disturbed concentration; disorientation; delusions; hallucinations; excitement; anxiety; restlessness; insomnia; nightmares; numbness, tingling, and paresthesias of the extremities; peripheral neuropathy; incoordination; ataxia; tremors; seizures; alteration in EEG patterns; extrapyramidal symptoms; tinnitus. *Anticholinergic:* Dry mouth; blurred vision; disturbance of accommodation; constipation; paralytic ileus; urinary retention; dilatation of urinary tract. *Allergic:* Skin rash; urticaria; photosensitization; edema of face and tongue. *Hematologic:* Bone marrow depression including agranulocytosis; leukopenia; eosinophilia; purpura; thrombocytopenia. *Gastrointestinal:* Nausea; epigastric distress; vomiting; anorexia; stomatitis; peculiar taste; diarrhea; parotid swelling; black tongue. *Endocrine:* Testicular swelling and gynecomastia in the male; breast enlargement and galactorrhea in the female; increased or decreased libido; elevated or lowered blood sugar levels. *Other:* Dizziness, weakness; fatigue; headache; weight gain or loss; increased perspiration; urinary frequency; mydriasis; drowsiness; jaundice; alopecia. *Withdrawal Symptoms:* Abrupt cessation after prolonged administration may produce nausea, headache, and malaise. These are not indicative of addiction.

OVERDOSAGE: All patients suspected of having taken an overdosage should be admitted to a hospital as soon as possible. Treatment is symptomatic and supportive. However, the intravenous administration of 1-3 mg of physostigmine salicylate has been reported to reverse the symptoms of tricyclic antidepressant poisoning. On this basis, in severe overdosage with perphenazine-amitriptyline combinations, symptomatic treatment of central anticholinergic effects with physostigmine salicylate should be considered.

For more detailed information, consult your MSD Representative or see full Prescribing Information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, Pa. 19486.

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Must vasodilators and therapy for other diseases come into conflict?

not if the vasodilator is

VASODILAN®

(ISOXSUPRINE HCl)

the compatible vasodilator... no treatment conflicts reported

The cerebral or peripheral vascular disease patient often has coexisting disease[1] which calls for another drug along with his vasodilator. It may be a hypoglycemic, miotic, antihypertensive, diuretic, anticoagulant, corticosteroid, or coronary vasodilator.

Vasodilan is not incompatible with any of these drugs—no treatment conflict has been reported. And, unlike other vasodilators, Vasodilan has not been reported to affect carbohydrate metabolism, liver function, or intraocular pressure—or to complicate treatment of diabetes, hypertension, peptic ulcer, glaucoma, or liver disease.

In fact, there are no known contraindications to the use of Vasodilan in recommended oral doses, other than that it should not be given in the presence of frank arterial bleeding or immediately postpartum.

1. Gertler, M. M., et al.: Geriatrics *25*:134-148 (May) 1970.

Indications: Based on a review of this drug by the National Academy of Sciences-National Research Council and/or other information, the FDA has classified the indications as follows:

Possibly Effective:

1. For the relief of symptoms associated with cerebral vascular insufficiency.
2. In peripheral vascular disease of arteriosclerosis obliterans, thromboangiitis obliterans (Buerger's Disease) and Raynaud's disease.
3. Threatened abortion.

Final classification of the less-than-effective indications requires further investigation.

Composition: Vasodilan tablets, isoxsuprine HCl, 10 mg. and 20 mg.

Dosage and Administration: 10 to 20 mg. three or four times daily.

Contraindications and Cautions: There are no known contraindications to oral use when administered in recommended doses. Should not be given immediately postpartum or in the presence of arterial bleeding.

Adverse Reactions: On rare occasions, oral administration of the drug has been associated in time with the occurrence of severe rash. When rash appears, the drug should be discontinued. Occasional overdosage effects such as transient palpitation or dizziness are usually controlled by reducing the dose.

Supplied: Tablets, 10 mg.—bottles of 100, 1000, 5000 and Unit Dose; 20 mg.—bottles of 100, 500 and Unit Dose.

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For nearly a quarter of a century, Soyalac has proven its value in promoting growth and development—as shown by extensive clinical data.

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CARDIOLOGIST—Board certified internist with subspecialty in cardiology needed for busy cardiology practice in Orange County, with excellent facilities and adjacent medical school. Send résumé to Box 9392, Western Journal of Medicine, 731 Market St., San Francisco, 94103.

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ORTHOPEDIST: Board certified or board eligible, for large multispecialty group. Department currently consists of seven orthopedists. Department and area expanding. Edward H. Start, MD, Chief of Orthopedics, The Permanente Clinic, 5055 North Greeley Ave., Portland, Oregon 97217.

PULMONARY DISEASE PHYSICIAN, certified, to associate with a Cardiologist in Orange County. Send curriculum vitae to: E. C. Gaulden, MD, 17541 Irvine Blvd., Tustin, CA, or call (714) 838-2655.

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INTERNIST—Four man corporation, two full time and two part time, want internist or general practitioner. Expanding with new Medical building in San Gabriel Valley growing area. Salary open, fringe benefits. Contact H. A. Chollet, MD, 430 W. Badillo, Covina, CA 91723; Phone (213) 331-9419.

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WANTED: Family Practitioner, Versatile Internist or Pediatrician, for new primary care facility in reconstructed housing development. Fluency in, or some facility with, Spanish is desirable. Close collaboration with large County hospital and medical school furnish excellent educational opportunities. The innovative aspects of this format for providing high quality medical care to an underserved defined population should provide gratification and challenge to the right physician. Salary is dependent upon qualifications. Liberal fringe benefits include vacation, sick leave, group insurance, college tuition for children. Location in Southern California provides easy access to mountains, desert and seashore under ideal weather conditions. Unsurpassed recreational, cultural, and educational resources. Send references to Norman Shrifter, MD, 1100 North Mission Road, Los Angeles, CA 90033.

STAFF PSYCHIATRIST—Community based total health care program. Team approach is used to provide full range of direct and indirect services to rural and urban communities. Located in the Central Valley close to San Francisco, Los Angeles, ocean and the mountains. Contact: J. Frank James, MD, 515 South Cedar Ave., Fresno, CA 93702, (209) 488-3747.

EXCELLENT IMMEDIATE OPPORTUNITY for Pulmonary Internist to join Board Certified Pulmonary Specialist in San Diego, California. Private practice includes office care, hospital consultations, and medical direction of Respiratory Therapy-Pulmonary Function Departments. Reply with curriculum vitae to: Jerry E. Fein, MD, 6355 Ridge Manor Ave, San Diego, CA 92120.

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OB/GYN RESIDENCY—Second year available July 1, 1975. Fully approved program. All qualified applicants urged to apply. Valid California license must be in hand. Salary $15,432 annually, plus fringe benefits. Contact Dr. Leroy Smale, Chairman, Kern General Hospital, 1830 Flower Street, Bakersfield, CA 93305.

STEINBECK COUNTRY: Innovative, progressive rural group practice located in the Salinas Valley has an immediate need for 2 Family Practitioners, a Pediatrician and an Internist with broad-based capabilities. In addition to 9 full-time physicians, the group has 11 consultants, representing a wide spectrum of the specialties, visiting on a routine basis. University affiliation with on-site teaching. Top fringe benefits, including competitive starting salary (1st year minimum of $34,000 guaranteed), and early affiliation. Brochure by return mail. Please call or send C.V. to: Duane F. Hyde, MD, Southern Monterey County Medical Group (A Professional Corporation), 210 Canal Street, King City, CA 93930; (408) 385-5471.

CARDIOLOGIST—Board certified or eligible in CD to join limited specialty Cardiology practice on Palos Verde Peninsula of Southern California. For information contact Joseph Nebolon, MD, 3440 W. Lomita Blvd., Torrance, CA 90505; (213) 530-1611.

(Continued on Page 25)

PHYSICIANS

Needed for part-time and full-time employment with Los Angeles County Dept. of Personnel Occupational Health Service. Clinical and/or administrative openings are in medical examination program. For further information, please contact Ronald Schwartz, MD, MPH, Associate Medical Director, Occupational Health Service Department of Personnel, Suite 500, 601 W. Fifth St., Los Angeles, CA 90017. Phone (213) 974-2663.

INTERNISTS, Board Certified or eligible; **FAMILY PRACTITIONERS;** for multi-specialty group on Island of Oahu. Also **PEDIATRICIAN** willing to do general practice for Island of Maui. Starting salary negotiable. Excellent fringe benefits. Write: Hawaii Permanente Medical Group, Inc., 1697 Ala Moana Blvd., Honolulu, Hawaii 96815.

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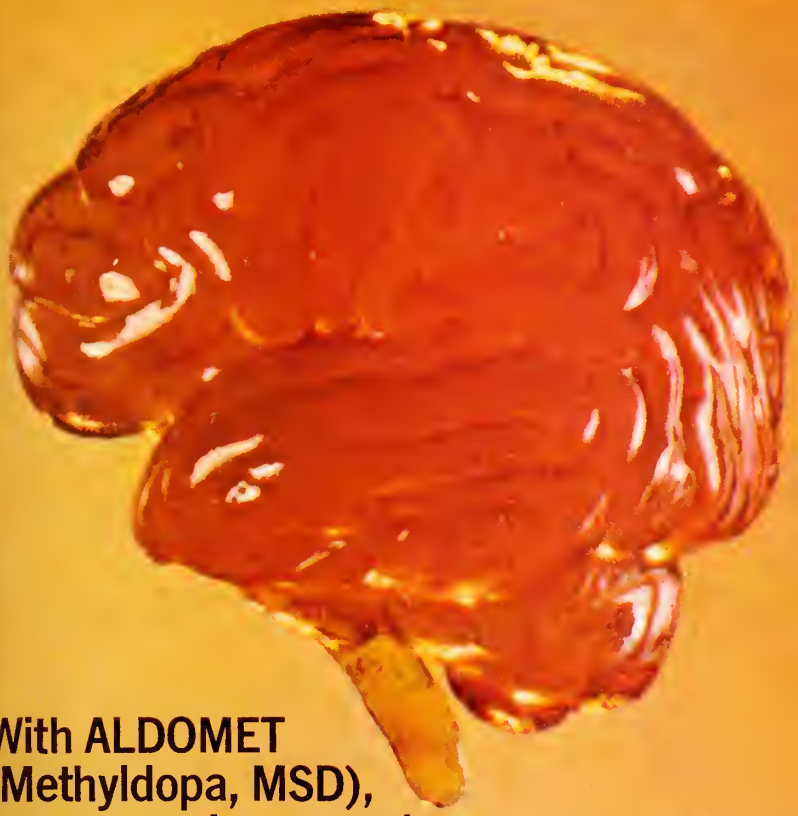
In most cases of sustained moderate hypertension, ALDOMET® (METHYLDOPA|MSD) usually offers more than effective lowering of blood pressure...

With ALDOMET (Methyldopa, MSD), existing renal function is usually unchanged

ALDOMET has no direct effect on renal function. When used in effective doses, ALDOMET usually does not reduce glomerular filtration rate, renal blood flow, or filtration fraction.

With ALDOMET (Methyldopa, MSD), cardiac output is generally unchanged

ALDOMET has no direct effect on cardiac function. When ALDOMET is used in effective doses cardiac output is usually maintained with no cardiac acceleration; in some patients the heart rate is slowed.



With ALDOMET (Methyldopa, MSD), symptomatic postural hypotension is infrequent

ALDOMET reduces both supine and standing blood pressure. Less frequent symptomatic postural hypotension is experienced with ALDOMET than with many other antihypertensive agents. Exercise hypotension and diurnal blood pressure variations rarely occur.

for sustained moderate hypertension

TABLETS, 250 mg and 500 mg

ALDOMET®
(METHYLDOPA|MSD)

a unique antihypertensive agent

Contraindications include active hepatic disease and known sensitivity to the drug. Use with caution in patients with a history of liver disease or dysfunction. Not recommended in pheochromocytoma or pregnancy.

It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed. For more details see the brief summary of prescribing information.

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For a brief summary of prescribing information, please see following page.

addendum

MSD
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to further simplify therapy for many patients

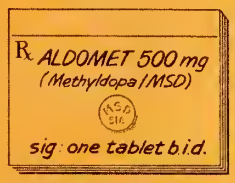
now available
ALDOMET® 500 mg
(METHYLDOPA|MSD)

- **often more practical to prescribe**
- **easier for patients to remember**

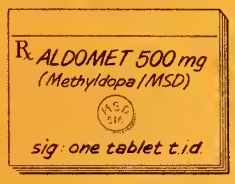
Now offered in addition to the standard 250-mg tablet, the new ALDOMET 500 mg tablet is a patient convenience. An especially important one, since in hypertension convenience of the dosage schedule is one factor that can make the difference in compliance of the patient. The minimum daily dose of ALDOMET is 250 mg b.i.d. The usual starting dose is 250 mg t.i.d. Dosage is adjusted as necessary by adding or deleting 250 mg or 500 mg at intervals of not less than two days. The maximum dose is 3.0 g per day.

Examples of b.i.d. or t.i.d. dosage convenience provided by ALDOMET 500 mg within the usual daily dosage range of 500 mg to 2.0 g:

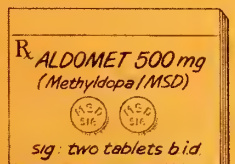
1.0-g daily dose =

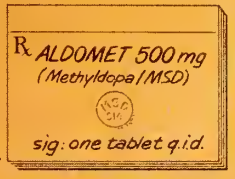


1.5-g daily dose =



2.0-g daily dose =





NOTE: Tablets shown are not actual size.

in sustained moderate hypertension

ALDOMET® (METHYLDOPA|MSD)

usually lowers blood pressure effectively

Contraindications: Active hepatic disease, such as acute hepatitis and active cirrhosis. Known sensitivity. Not recommended in pheochromocytoma. Unsuitable in mild or labile hypertension responsive to mild sedation or thiazide therapy. Use cautiously in patients with history of previous liver disease or dysfunction.

Warnings: It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed. Read this section carefully to understand these reactions.

With prolonged methyldopa therapy, 10% to 20% of patients develop a positive direct Coombs test, usually between six and twelve months of therapy. Lowest incidence is at daily dosage of 1 g or less. This on rare occasions may be associated with hemolytic anemia, which could lead to potentially fatal complications. One cannot predict which patients with a positive direct Coombs test may develop hemolytic anemia. Prior existence or development of a positive direct Coombs test is not in itself a contraindication to use of methyldopa. If a positive Coombs test develops during methyldopa therapy, determine whether hemolytic anemia exists and whether the positive Coombs test may be a problem. For example, in addition to a positive direct Coombs test there is less often a positive indirect Coombs test which may interfere with cross matching of blood.

At the start of methyldopa therapy, it is desirable to do a blood count (hematocrit, hemoglobin, or red cell count) for a baseline or to establish whether there is anemia. Periodic blood counts should be done during therapy to detect hemolytic anemia. It may be useful to do a direct Coombs test before therapy and at six and twelve months after the start of therapy. If Coombs-positive hemolytic anemia occurs, the cause may be methyldopa and the drug should be discontinued. Usually the anemia remits promptly. If not, corticosteroids may be given and other causes of anemia should be considered. If the hemolytic anemia is related to methyldopa, the drug should not be reinstituted. When methyldopa causes Coombs positivity alone or with hemolytic anemia, the red cell is usually coated with gamma globulin of the IgG (gamma G) class only. The positive Coombs test may not revert to normal until weeks to months after methyldopa is stopped.

Should the need for transfusion arise in a patient receiving methyldopa, both a direct and an indirect Coombs test should be performed on his blood. In the absence of hemolytic anemia, usually only the direct Coombs test will be positive. A positive direct Coombs test alone will not interfere with typing or cross matching. If the indirect Coombs test is also positive, problems may arise in the major cross match and the assistance of a hematologist or transfusion expert will be needed.

Fever has occurred within first three weeks of therapy, sometimes with eosinophilia or abnormalities in liver function tests, such as serum alkaline phosphatase, serum transaminases (SGOT, SGPT), bilirubin, cephalin cholesterol flocculation, prothrombin time, and bromsulphalein retention. Jaundice, with or without fever, may occur, with onset usually in the first two to three months of therapy. In some patients the findings are consistent with those of cholestasis. Rarely fatal hepatic necrosis has been reported. These hepatic changes may represent hypersensitivity reactions; periodic determination of hepatic function should be done particularly during the first six to twelve weeks of therapy or whenever an unexplained fever occurs. If fever, abnormalities in liver function tests, or jaundice appear, stop therapy with methyldopa. If caused by methyldopa, the temperature and abnormalities in liver function characteristically have reverted to normal when the drug was discontinued. Methyldopa should not be reinstituted in such patients.

Rarely, reversible reduction in leukocyte count with primary effect on granulocytes has been seen. Reversible thrombocytopenia has occurred rarely. When used with other antihypertensive drugs, potentiation of antihypertensive effect may occur.

Use in Pregnancy and Childbearing Age—Not recommended in pregnancy. In women of childbearing age, weigh potential benefits against possible fetal hazards.

Precautions: Methyldopa may interfere with measurement of: uric acid by the phosphotungstate method, creatinine by the alkaline picrate method, and SGOT by colorimetric methods. Since methyldopa causes fluorescence in urine samples at the same wavelengths as catecholamines, spuriously high levels of urinary catecholamines may be reported. This will interfere with the diagnosis of pheochromocytoma. Stop drug if involuntary choreoathetotic movements occur in patients with severe bilateral cerebrovascular disease. Patients may require reduced doses of anesthetics; hypotension occurring during anesthesia usually can be controlled with vasopressors. Hypertension has occurred after dialysis in patients on methyldopa because the drug is removed by this procedure.

Adverse Reactions: Sedation, usually transient, may be seen during initial therapy or when dosage is increased. Headache, asthenia, or weakness may be noted as early, transient symptoms. Symptoms associated with effective lowering of blood pressure are occasionally seen and include dizziness, lightheadedness, and symptoms of cerebrovascular insufficiency. Angina pectoris may be aggravated. Symptoms of orthostatic hypotension may occur; if symptoms occur, reduction of dosage is suggested. Bradycardia, nasal stuffiness, mild dryness of mouth, and gastrointestinal symptoms including distention, constipation, flatus, and diarrhea occur occasionally; these generally can be relieved by reducing dosage. Nausea and vomiting have been reported in only a few patients. Sore tongue or "black tongue," pancreatitis, and inflammation of salivary glands may occur.

Weight gain and edema occur infrequently and are relieved by administering a thiazide diuretic; if edema progresses or signs of pulmonary congestion appear, discontinue drug. A rise in BUN has been observed. Other rare reactions include breast enlargement, lactation, impotence, decreased libido, skin rash, mild arthralgia, myalgia, paresthesias, Bell's palsy, parkinsonism, psychic disturbances including nightmares, reversible mild psychoses or depression. Urine exposed to air after voiding may darken because of breakdown of methyldopa or its metabolites.

Note: Dosage should be limited initially to 500 mg daily when following previous antihypertensive agents other than thiazides. Maximal recommended daily dose is 3.0 g. Patients with impaired renal function may respond to smaller doses than patients with normal kidney function. Syncope in older patients has been related to increased sensitivity in those with advanced arteriosclerotic vascular disease; this may be avoided by lower doses. Tolerance occasionally seen either early or late, but more likely between second and third month after initiation of therapy; increased dosage or combined therapy with a thiazide frequently restores effective control.

How Supplied: Tablets, containing 250 mg methyldopa each, in single-unit packages of 100 and bottles of 100 and 1000; Tablets, containing 500 mg methyldopa each, in single-unit packages of 100 and bottles of 100.

For more detailed information, consult your MSD representative or see full prescribing information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, Pa. 19486

MSD MERCK SHARP & DOHME

(Continued from Page 21)

PHYSICIANS WANTED

SAROYAN COUNTRY: Central Calif., near Sierras for skiing and year-round recreation; great opportunity for **RADIOLOGISTS** with subspecialty training in 250-bed teaching hospital, building program under way; 2 Radiologists associated in practice, Dept. of 30, soon to be affiliated with University of California, S.F. Salary negotiable. Write—Dr. Justin L. Williams, Valley Medical Center, Fresno, CA 93702.

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IN GONORRHEA

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Gonorrhea, according to the national Center for Disease Control, is, if the parenteral route is chosen, most effectively treated with aqueous procaine penicillin G. In uncomplicated cases, administration of 4.8 million units together with 1 gram oral probenecid, given at least 30 minutes prior to injection, is recommended.

Indications: In treatment of moderately severe infections due to penicillin G-sensitive microorganisms sensitive to the low and persistent serum levels common to this particular dosage form. Therapy should be guided by bacteriological studies (including sensitivity tests) and by clinical response.

NOTE: When high sustained serum levels are required use aqueous penicillin G, IM or IV.

The following infection will usually respond to adequate dosages of intramuscular procaine penicillin G.—*N. gonorrhoeae:* acute and chronic (without bacteremia).

For deep intramuscular injection only.

Contraindications: Previous hypersensitivity reaction to any penicillin.

Warnings: Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy.

Serious anaphylactoid reactions require immediate emergency treatment with epinephrine. Oxygen and intravenous corticosteroids should also be administered as indicated.

Although anaphylaxis is more frequent following parenteral therapy it has occurred in patients on oral penicillins. These reactions are more apt to occur in individuals with a history of sensitivity to multiple allergens.

There have been well documented reports of individuals with a history of penicillin hypersensitivity reactions who have experienced severe hypersensitivity reactions when treated with a cephalosporin. Before therapy with a penicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, and other allergens. If an allergic reaction occurs, the drug should be discontinued and the patient treated with the usual agents e.g., pressor amines, antihistamines and corticosteroids.

Precautions: Use cautiously in individuals with histories of significant allergies and/or asthma.

Carefully avoid intravenous or intraarterial use, or injection into or near major peripheral nerves or blood vessels, since such injections may produce neurovascular damage.

A small percentage of patients are sensitive to procaine. If there is a history of sensitivity, make the usual test: Inject intradermally 0.1 cc. of a 1 to 2 percent procaine solution. Development of an erythema, wheal, flare or eruption indicates procaine sensitivity. Sensitivity should be treated by the usual methods, including barbiturates, and procaine penicillin preparations should not be used. Antihistaminics appear beneficial in treatment of procaine reaction.

The use of antibiotics may result in overgrowth of nonsusceptible organisms. Constant observation of the patient is essential. If new infections due to bacteria or fungi appear during therapy, discontinue penicillin and take appropriate measures.

If allergic reaction occurs, withdraw penicillin unless, in the opinion of the physician, the condition being treated is life threatening and amenable only to penicillin therapy.

When treating gonococcal infections with suspected primary or secondary syphilis, perform proper diagnostic procedures, including darkfield examinations. In all cases in which concomitant syphilis is suspected, perform monthly serological tests for at least four months.

Adverse Reactions: (Penicillin has significant index of sensitization) skin rashes, ranging from maculopapular eruptions to exfoliative dermatitis; urticaria; serum sickness-like reactions, including chills, fever, edema, arthralgia and prostration. Severe and often fatal anaphylaxis has been reported. (See "Warnings.")

As with other antisyphilitics, Jarisch-Herxheimer reaction has been reported.

Administration and Dosage: Administer only by *deep intramuscular injection,* in upper outer quadrant of buttock. In infants and small children, midlateral aspect of thigh may be preferable. When doses are repeated, vary injection site. Before injection, aspirate to be sure needle bevel is not in blood vessel. If blood appears, remove needle and inject in another site.

Although some isolates of *Neisseria gonorrhoeae* have decreased susceptibility to penicillin, this resistance is relative, not absolute, and penicillin in large doses remains the drug of choice. Physicians are cautioned not to use less than recommended doses.

Gonorrheal infections (uncomplicated)—Men or Women: 4.8 million units intramuscularly divided into at least two doses and injected at different sites at one visit, together with 1 gram of oral probenecid, preferably given at least 30 minutes prior to injection.

NOTE: Treatment of severe complications of gonorrhea should be individualized using large amounts of short-acting penicillin. Gonorrheal endocarditis should be treated intensively with aqueous penicillin G. Prophylactic or epidemiologic treatment for gonorrhea (male and female) is accomplished with same treatment schedules as for uncomplicated gonorrhea.

Retreatment: The National Center for Disease Control, Venereal Disease Branch, U.S. Dept. H.E.W. recommends:

Test cure procedures at approximately 7-14 days after therapy. In the male, a gram-stained smear is adequate if positive; otherwise, a culture specimen should be obtained from the anterior urethra. In the female, culture specimens should be obtained from both the endocervical and anal canal sites.

Retreatment in males is indicated if urethral discharge persists 3 or more days following initial therapy and smear or culture remains positive. Follow-up treatment consists of 4.8 million units I.M. divided in 2 injection sites at single visit.

In uncomplicated gonorrhea in the female, retreatment is indicated if follow-up cervical or rectal cultures remain positive for *N. gonorrhoeae.* Follow-up treatment consists of 4.8 million units daily on 2 successive days.

Syphilis: all gonorrhea patients should have a serologic test for syphilis at the time of diagnosis. Patients with gonorrhea who also have syphilis should be given additional treatment appropriate to the stage of syphilis.

Composition: Each disposable syringe 2,400,000 units (4-cc. size) contains procaine penicillin G in a stabilized aqueous suspension with sodium citrate buffer, and as w/v approximately 0.5% lecithin, 0.5% carboxymethylcellulose, 0.5% povidone, 0.1% methylparaben, and 0.01% propylparaben. The multiple-dose 10-cc. vial contains per cc. 300,000 units procaine penicillin G in a stabilized aqueous suspension with sodium citrate buffer and approximately 7 mg. lecithin, 2 mg. carboxymethylcellulose, 3 mg. povidone, 0.5 mg. sorbitan monopalmitate, 0.5 mg. polyoxyethylene sorbitan monopalmitate, 1.2 mg. methylparaben, and 0.14 mg. propylparaben.

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INJECTION
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Syphilis is preferably treated with benzathine penicillin G, which is also the drug of choice for prophylaxis after exposure. Administration of 2.4 million units (1.2 million in each buttock) usually cures most cases of primary, secondary and latent syphilis with negative spinal fluid.

Indications: In treatment of infections due to penicillin G-sensitive microorganisms that are susceptible to the low and very prolonged serum levels common to this particular dosage form. Therapy should be guided by bacteriological studies (including sensitivity tests) and by clinical response.

The following infections will usually respond to adequate dosage of intramuscular benzathine penicillin G.—Venereal infections: Syphilis, yaws, bejel and pinta.

For deep intramuscular injection only.

Contraindications: Previous hypersensitivity reaction to any penicillin.

Warnings: Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported. Anaphylaxis is more frequent following parenteral therapy but has occurred with oral penicillins. These reactions are more apt to occur in individuals with history of sensitivity to multiple allergens.

Severe hypersensitivity reactions with cephalosporins have been well documented in patients with history of penicillin hypersensitivity. Before penicillin therapy, carefully inquire into previous hypersensitivity to penicillins, cephalosporins and other allergens. If allergic reaction occurs, discontinue drug and treat with usual agents, e.g., pressor amines, antihistamines and corticosteroids.

Precautions: Use cautiously in individuals with histories of significant allergies and/or asthma.

Carefully avoid intravenous or intraarterial use, or injection into or near major peripheral nerves or blood vessels, since such injection may produce neurovascular damage.

In streptococcal infections, therapy must be sufficient to eliminate the organism; otherwise the sequelae of streptococcal disease may occur. Take cultures following completion of treatment to determine whether streptococci have been eradicated.

Prolonged use of antibiotics may promote overgrowth of nonsusceptible organisms including fungi. Take appropriate measures should superinfection occur.

Adverse Reactions: Hypersensitivity reactions reported are skin eruptions (maculopapular to exfoliative dermatitis), urticaria and other serum sickness reactions, laryngeal edema and anaphylaxis. Fever and eosinophilia may frequently be only reaction observed. Hemolytic anemia, leucopenia, thrombocytopenia, neuropathy and nephropathy are infrequent and usually associated with high doses of parenteral penicillin.

As with other antisyphilitics, Jarisch-Herxheimer reaction has been reported.

Administration and Dosage: Venereal infections—

Syphilis—Primary, secondary and latent—2.4 million units (1 dose).

Late (tertiary and neurosyphilis)—2.4 million units at 7 day intervals for three doses.

Congenital—under 2 years of age, 50,000 units/Kg. body weight; ages 2-12 years, adjust dosage based on adult dosage schedule.

(Shake multiple-dose vial vigorously before withdrawing the desired dose.) Administer by **deep intramuscular injection** in the upper outer quadrant of the buttock. In infants and small children, the midlateral aspect of the thigh may be preferable. When doses are repeated, vary the injection site. Before injecting the dose, aspirate to be sure needle bevel is not in a blood vessel. If blood appears, remove the needle and inject in another site.

Composition: Units benzathine penicillin G (as active ingredient): 2,400,000 units in 4-cc. single dose disposable syringe. Each disposable syringe also contains in aqueous suspension with sodium citrate buffer, as w/v approximately 0.5% lecithin, 0.6% carboxymethylcellulose, 0.6% povidone, 0.1% methylparaben, and 0.01% propylparaben. 300,000 units per cc.—10-cc. multi-dose vial. Each cc. also contains sodium citrate buffer, approximately 6 mg. lecithin, 3 mg. povidone, 1 mg. carboxymethylcellulose, 0.5 mg. sorbitan monopalmitate, 0.5 mg. polyoxyethylene sorbitan monopalmitate, 1.2 mg. methylparaben, and 0.14 mg. propylparaben.

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Seminars in Infectious Disease

Perinatal and Neonatal Infections

JOSEPH W. ST. GEME, JR., MD, *Torrance, California*

TWO IMPORTANT DEFINITIONS should be made before discussing the more common acquired bacterial and viral infections of very early infancy. *Perinatal* infections may be characterized by their appearance within the first few days after birth or the first two weeks of life. Although perhaps an arbitrary exercise in semantics, *neonatal* infections may be defined as infections which occur later, between three and six weeks of age. This paper will discuss the significance of the separation of infections of very early infancy into these two categories and the importance of this separation from a conceptual viewpoint. Infections, which (by strict definition of the word congenital) are acquired transplacentally during embryonic and fetal life, will not be discussed.

Clinical Manifestations

The clinical signs of perinatal and neonatal infections are similar and uniquely vague, particularly if the later infection occurs in a premature infant. The physiologic fragility of thermal regulation in the newborn, most notably premature infants, conditions the occasional appearance of hypothermia—rather than fever—with sepsis. Unexplained apnea may be the only signal of infection, as was witnessed in two recent outbreaks of nosocomial neonatal echovirus infection which occurred in infant special care units.[1,2] The cerebropathic element of perinatal and neonatal infections may be discerned by subtle motor lapses rather than overt tonic-clonic convulsive episodes. Idiopathic hyperbilirubinemia of the indirect unconjugated type may indicate early perinatal infection, and because of concomitant cholestatic hepatitis late neonatal infection, particularly of the urinary tract, may be associated with elevation of direct-reacting conjugated bilirubin in the serum.[3,4] Early infections seem to impair hepatocytic conjugating functions, while late infections disrupt canalicular secretory processes and may be confused with biliary atresia or neonatal hepatitis. It is difficult to emphasize adequately the subtlety of failure-to-thrive in a septic infant, the importance of detecting this early sign of abnormality and the incalculable value of experienced nursing personnel who are ordinarily the first to sense minor alterations of infant behavior (for instance, poor suck, more voluminous regurgitation, respiratory irregularity, looser stools, transient cyanosis and hypoactivity). Physical findings of bacteremia are few, and even during late infection—when meningitis may also accompany systemic infection—one may not be able to elicit signs of meningeal irritation.

Incidence

Infection occurs in two peaks, the early perinatal infection and the late neonatal infection, as defined above. The overall incidence of sepsis during early infancy ranges from 1 in 500 to 1 in 1,600 live births.[5,6] In our experience[7] the number of perinatal infections is almost twice that of

From the Department of Pediatrics, Harbor General Hospital, Torrance, and University of California, Los Angeles, School of Medicine.

Submitted, revised, August 30, 1974.

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neonatal infection and the analysis of bacterial meningitis in the Collaborative Perinatal Research Study supports this observation.[6]

The risk of developing significant perinatal bacterial infection is increased ten times if prolonged rupture of amnionic membranes (beyond 12 to 24 hours) has occurred, and increased 100 times if febrile amnionitis has complicated prolonged membrane rupture.[8] In the event of prolonged membrane rupture and the intensified danger of maternal amnionitis, identification of the pathogen and the infant at risk may be pursued by culture of the vagina and cord blood, and of the gastric contents, axilla and umbilicus of the suspect infant. Hosmer and Sprunt[9] have pointed out the problems of getting significant clinical and microbial data by these techniques and stress the importance of duplicate blood cultures of the infant from different sites. If the same organism is recovered from most of these culture sites, certainly from blood, a presumptive diagnosis of high risk latent infection might be made and precise antimicrobial therapy begun.

Scanlon[10] has recently reported that with a Gram smear of the auditory canal, a truly infected infant—born of a mother with ruptured and possibly infected membranes—may be identified simply by searching for three or more polymorphonuclear leukocytes per high power field. A lumbar puncture should be included when considering infection in a very young infant, since in 30 to 50 percent of these infants meningitis is present or meningitis in addition to bacteremia.[5] When the puerperium is complicated by prolonged membrane disruption and maternal amnionitis, an infant should also be evaluated with lumbar puncture—particularly those infants with minimal symptoms, and perhaps even those without symptoms because the risk of their acquisition of infection may be as high as 10 percent.[8]

In approximately 1 percent of newborn infants, cytomegalovirus is excreted in urine.[11] This astonishingly high incidence of infection seems to be related to the shedding of this virus in the cervical secretions of 10 to 20 percent of women during the final trimester of pregnancy.[12-14] The greater incidence of cervical shedding of cytomegalovirus during the later stages of gestation may reflect the cumulative effect of pregnancy on reactivation of virus replication from latent sites of repose in genital tissues. In about 1 to 5 percent of nonpregnant women, cytomegalovirus is shed from the cervix.[15] Fortunately, this rather common perinatal virus infection is usually subclinical and associated with a generally favorable outcome during the ensuing years of childhood.[16,17]

Perinatal herpes simplex virus infection is estimated to occur in one of 7,000 births.[18] Since the type 2 genital strain of herpes simplex virus, which is the predominant species in these early perinatal infections, may be transmitted by the venereal mode, the incidence of this serious illness has probably risen over the past few years. As is true for maternal cytomegalovirus infections, herpes simplex virus type 2 can be isolated from the genital lesions and secretions of less than 1 percent of nongravid women but rises to a shed rate of 1 to 3 percent in pregnant women at term.[19] The speculation that pregnancy alters the relationship between the latent state and reactivation of virus is an attractive consideration for this virus also.

Approximately 70 percent of newborn infants with herpes simplex virus infection die, and the prognosis for normal cerebral function of survivors is poor. Effective antiviral drugs may ultimately modify these discouraging facts. On the other hand, specific antibiotic therapy has reduced the once awesome mortality of perinatal and neonatal bacterial infection from 90 percent to between 13 and 45 percent.[5] Unfortunately, the morbidity of bacterial infection persists and circumscribes varied neurologic problems, primarily seizures, hydrocephalus, mental retardation and learning disorders. The frequency of these overt and subtle neurologic sequelae reflects the species of bacterial pathogen and may be as high as 90 percent following Gram-negative bacterial infection and 50 percent following Gram-positive infection.[20]

Cause of Infection

Perinatal infections arise from contact with potential pathogens in the cervicovaginal canal. This may be illustrated by the striking occurrence of the initial cutaneous lesion of herpes simplex virus infection on the vertex of the scalp in many of the infants we have seen. It is as if a natural vaccination occurred as the presenting part was compressed by the cervical os and then the vaginal vault during the first and second stage of labor. Unfortunately, the virus involved is not an attenuated strain. Although it is difficult to prove, on rare occasions perinatal bacterial and viral infections may result from transcervical and transam-

nionic spread of pathogens despite the integrity of amnionic membranes.

Neonatal infections arise from the environment of care—most notably from isolettes, respirators, umbilical catheters, other infants and occasionally hospital personnel. All of these environmental elements are intensified if a major surgical procedure is carried out in a young infant. Fifty percent of umbilical arterial and venous catheter tips left *in situ* for several days yield bacteria, largely staphylococcal and pseudomonas organisms, when they are withdrawn and cultured.[21,22] About 10 percent of infants whose umbilical catheters have become pyogenic foci fail to clear the bacteria and develop significant bacteremia. A further alarming example of nosocomial infectious problems within neonatal intensive care units has been the recent observation of serious outbreaks of infection with kanamycin-resistant Klebsiella species.[23-25] The reservoir of infection in these outbreaks has been the infants themselves and nursing personnel have played an enhancing role by presumed and occasionally verified manual transmission of the pathogen.

The neonatal intensive care unit is a particularly provocative setting for the evolution of later neonatal bacterial infections. A varied assortment of infants with serious medical and surgical problems reside in these units for extended periods of time. There is widespread use of isolettes, respirators and vascular catheterization for monitoring and therapeutic purposes. The uniform and usually appropriate use of antibiotics within special care units represents a potentially powerful force for selection of resistant pathogens. The recent outbreaks of antibiotic-resistant Gram-negative bacillary infection are not surprising. In addition to the vigorous and continued cleansing of isolettes and the tubing and nebulizing components of respirators, and the substitution of peripheral needles for central catheters in the implementation of fluid and metabolic therapy, it may become necessary to restrict antimicrobial therapy more rigidly only to those infants in whom there is documented bacterial infection. Since the patterns of admission to intensive care units ordinarily preclude strict adherence to a cohort system of infant location within the unit, the cohort deployment of nursing personnel may prove to be a necessary adjustment to prevent and contain serious nosocomial infection.

An interesting example of nosocomial neonatal bacterial illness where nursing personnel may have played a major role is the emergence of exfoliative toxin-producing Staphylococcus aureus infection.[26] The phage type 71 straphylococcal infection produces Ritter's disease and occurs as a late neonatal infection. The organism is acquired in regular full-term nursery units during the short time span of modern newborn care, apparently from nursing personnel with nasal colonization by this pathogen. The epidemiology and ecology of this new neonatal staphylococcal pathogen is similar to that of the phage type 80/81 of the late 1950's.[27]

Perinatal Pathogens

Infections occurring during the first few days to two weeks after birth evolve from contact with potential pathogens in the cervicovaginal flora. These bacteria, fungi and viruses are of maternal origin and include Escherichia coli, group B beta hemolytic streptococci, gonococci, Treponema pallidum, Listeria monocytogenes, Bacteroides species, Candida albicans, cytomegalovirus and herpes simplex virus type 2. Prolonged rupture of the amnionic membranes before birth intensifies the risk of infant infection. The increase in sexual promiscuity during the past decade has also increased the incidence of perinatal infection. In addition to gonococcal and luetic infection, venereal transmission has been shown to exist for cytomegalovirus and the type 2 genital strain of herpes simplex virus.[28,29] As has been suggested, prolonged gestation permits the nurturing of microbial replication and the reactivation of some viruses.

The onset of perinatal infection, either very soon after birth or seven to 14 days later, may reflect the effect of differing inocula of these cervicovaginal pathogens on the incubation period of septic illness in infants.

An intriguing change in the pattern of pathogens has occurred during the past 20 years. The group B beta hemolytic streptococcus, a well recognized vaginal streptococcus and a rare cause of sepsis in the newborn in the past, has become a predominant pathogen in neonatal units throughout the country.[30] The incidence of group B beta hemolytic streptococcal shedding in the vagina may be as high as 30 percent in pregnant women.[31] The usual carrier rate for this organism in pregnant and nonpregnant women is approximately 5 to 10 percent, although Franciosi and colleagues[32] have suggested that the possibly more virulent

group B streptococcal types Ia, Ib and Ic may be substituted during late gestation for the ordinarily prevalent type III.

Neonatal Pathogens

The organisms producing these late infections, between three and six weeks after birth, arise primarily from the environment of care within the hospital or the home, although some of these infections are caused by lingering pathogens of earlier maternal origin. In our own experience only a third of all infections during the first two months of life occur during this later three to six week period. The prominent pathogens include Klebsiella, Aerobacter and Proteus species; Staphylococcus aureus; phage type 80/81 and 71; meningococci; Hemophilus influenzae; Pseudomonas aeruginosa; Candida albicans; group B coxsackieviruses; echoviruses; influenza virus; parainfluenza viruses and respiratory syncytial virus.

The occasional meningococcal and Hemophilus influenzae infections reflect the absence of transplacental maternal antibody in the sera of these young infants. The increasing incidence of Hemophilus influenzae infection emphasizes the changing pattern of immunity in adults. In the 1930's, 90 percent of cord blood contained Hemophilus influenzae bactericidal antibody, but in the 1970's only 10 percent of cord blood contained antibody.[33] Analysis of peripheral blood samples from mothers has revealed that only 25 percent contain bactericidal antibody.[33] Widespread antibiotic therapy has apparently diminished the natural immunity of adults acquired by repeated unchecked Hemophilus influenzae infections during the preantibiotic era.

Pseudomonas infections are rare, fortunately, as continued surveillance and eradication of the nosocomial sources of this important water-bug in isolettes, respirators and handwashing facilities has curbed significant outbreaks within neonatal units. Water bugs were an important and serious cause of epidemic, nosocomial neonatal infection in the early 1960's, with widespread contamination of standard equipment and plumbing components of routine full-term and preterm infant care units.[34-37] The rapid attack on this problem with simple adaptation of improved housekeeping techniques, better sanitation and more fastidious decontamination of equipment proved successful and timely, since neonatal intensive care units were just beginning to develop.[38]

Candidal neonatal infections are on the rise as a result of increasing implementation of parenteral hyperalimentation with central venous catheters.[39] We have seen several infants with widespread visceral and embolic candidemic disease, all of whom have responded satisfactorily to vigorous amphotericin therapy.[40] Clearly, these candidal neonatal infections evolve as the cutaneous barriers and natural resistance of the infant host are altered. These fungi arise from the infant or the immediate environment, although maternal vaginal candidal organisms usually seed the gastrointestinal tract of infants at birth.

We seldom witness the form of perinatal group B coxsackievirus infection which was described in the earlier literature, heralded by maternal symptoms at the time of parturition with subsequent fulminant illness in the infant.[41] Frequently, infants are admitted to special care units with the onset of late neonatal coxsackievirus or echovirus infection, characterized by unexplained fever or overt aseptic meningitis. These viral infections are usually benign, particularly in full-term infants, and often misdiagnosed as obscure or partially treated bacterial meningitis.[42] If these infections are examined by careful virologic techniques, we suspect that they will comprise a substantial component of late neonatal infection during the summer and fall months. These viruses may spread within special infant care units as nosocomial infections and although the afflicted host is often a preterm infant the outcome is rarely fatal.[1,2,43,44]

Outbreaks of febrile acute respiratory illness have occurred in preterm infant units caused by adenoviruses,[45] echoviruses,[46] parainfluenza viruses,[47] and respiratory syncytial virus.[48] The dissemination of these respiratory virus infections within preterm infant units may be far reaching, since these infants are kept in these units for prolonged periods and the incubation-transmission interval from one infant to another may be a relatively brief three to seven days. Recently, an outbreak of influenza was observed in a newborn nursery in Montreal, one of the few outbreaks from this cause ever described.[49]

A unique, late neonatal Escherichia coli infection is the syndrome of bacteremia, pyelonephritis, cholestatic hepatitis and direct hyperbilirubinemia.[3,4] As mentioned before, this illness may be confused with biliary atresia or neonatal hepatitis. Perinatal Escherichia coli sepsis during the early days of life may produce indirect hyperbilirubinemia.

Group B streptococcal infection may also ap-

pear as a late neonatal infection.[30,32,50,51] These streptococci may represent persisting maternal organisms acquired at birth, or possibly pathogens newly acquired from colonized infant cohorts.[31]

Factors of Host Resistance

In our experience, a third of the cases of perinatal and neonatal septicemia occur in preterm infants.[7] This is a uniform observation throughout the country and must be considered in the light of the fact that only 10 percent of all births are preterm.[5,6] An explanation for this discrepancy may be derived in part by examination of the various facets of innate and adaptive resistance to bacterial, fungal and viral infection. Although there is some disagreement,[52,53] the polymorphonuclear leukocyte of the preterm infant is intrinsically capable of undertaking normal phagocytosis and intracellular bacterial killing. Lower levels of antibody and complement in the serum of preterm infants account for impaired leukocytic function in vitro when the leukocyte and serum of preterm infants are tested together.[54-57] Defects do exist in the chemotactic responses of newborn leukocytes.[58] So, there is a problem with the important inflammatory response, but it is not known whether there is a difference in this regard between preterm and full-term infants. Lymphocyte or T-cell mediated cellular immunity, particularly important in the control of fungal and viral infections, is no more diminished in preterm than full-term infants.[59-61] Levels of serum immunoglobulin G (IgG) and immunoglobulin M (IgM) and opsonizing and neutralizing antibody of maternal transplacental origin, are somewhat lower in the preterm infant.[55,57,62,63] However, the ability of the low birth weight host to develop antibody is sufficient and comparable to the full-term infant.[64-66] Dealing with bacterial infection, IgG opsonins participate in the phagocytic killing of Gram-positive organisms, while IgM antibodies in concert with complement destroy Gram-negative organisms by lysis. IgM and, to a lesser extent, IgG antibodies also opsonize Gram-negative bacilli for phagocytosis. As has been pointed out, complement levels are lower in the preterm infant, and complement seems to play the major role not only in bacterial lysis and opsonization but also polymorphonuclear leukocytic chemotaxis.[57,58,67] Immature and preterm erythrocytes contain lower levels of 2, 3-diphosphoglycerate and are consequently less able to release oxygen to tissues.[68] Oxygen is vitally important in the key metabolic steps prerequisite to successful intraleukocytic kill of bacteria in infected tissues.[69]

The poorly understood blood-brain barrier is suspect in preterm infants and may be an important factor in the development of meningitis with perinatal and neonatal bacteremia, intensifying the seriousness of the sequelae of these infections during early infancy.

Ecologic, environmental and nosocomial phenomena may be considered strange bedfellows for a discussion of host resistance to infection in preterm infants. However, preterm infants are the most frequent recipients of umbilical catheters, are most frequently exposed to the respiratory and the toxic effect of oxygen on intrapulmonary phagocytic and ciliary function, are most frequently produced by pregnancies complicated by prolonged rupture of membranes and are kept in a hospital milieu—often an intensive care milieu—for the longest periods of time. Preterm infants are also the most frequent subjects of significant surgical procedures, attended by prolonged antibiotic manipulation of microbial flora, intensive violation of integument by parenteral therapeutic ventures and drainage of cavitary operative sites.

Therapy

With the recent emergence of group B beta hemolytic streptococcal perinatal and neonatal infection, some clinics have substituted penicillin for ampicillin as the antimicrobial agent directed at Gram-postive pathogens.[70] Continued study of group B streptococcal infection throughout the country suggests that there is no significant difference in the therapeutic efficacy of either antibiotic.[50,71] Kanamycin has been the usual accompanying antibiotic in the management of perinatal and neonatal sepsis, targeted for the Gram-negative spectrum of the common pathogens.

Recently, there has been some unrest about kanamycin in some sections of the country because of the gradual emergence of kanamycin-resistant Escherichia coli during the past 10 years.[72] McCracken[72] has reported that 1 to 10 percent of blood culture isolates in his clinic were resistant to kanamycin from 1963 to 1967, whereas from 1970 to 1971, 30 percent of such isolates were resistant. A survey of seven other neonatal units throughout the country disclosed that 20 to 30 percent of Escherichia coli were resistant to kanamycin and ampicillin. Only 5 percent of Escherichia

coli were resistant to gentamicin and polymyxin B. However, other neonatal care centers report continued susceptibility of the majority of coliform and other Gram-negative pathogens to kanamycin.[73] The practical conclusion which may be derived from these observations is that personnel in each neonatal unit must continue to examine the antimicrobial susceptibility of the pathogens recovered from its patients.

We have been concerned about the diffusion of kanamycin into the cerebrospinal fluid.[74] Although the data of Eichenwald[75] document adequate levels of kanamycin in the spinal fluid of infants with meningitis, our pharmacologic studies indicated that its levels in spinal fluid may be inadequate to eradicate Gram-negative pathogens. The substitution of gentamicin for kanamycin must be conducted usually with intrathecal administration if one is dealing with meningitis, since the spinal fluid concentration of gentamicin is quite low following parenteral therapy. The same pharmacologic principle obtains if polymyxin B is used to treat resistant Gram-negative organisms.

Our usual therapeutic strategy for apparent perinatal and neonatal sepsis involves the use of ampicillin and kanamycin after the procurement of blood, urine and spinal fluid cultures. If the spinal fluid is grossly purulent, intrathecal gentamicin or polymyxin is administered at the time of the initial lumbar puncture. Also, if the spinal fluid is visibly infected at the outset, we repeat the lumbar puncture 24 hours after the initiation of antimicrobial treatment to determine whether the pathogens have been eradicated from the spinal fluid. We consider this maneuver an *in vivo* antibiotic sensitivity test. If pathogens persist in the spinal fluid we begin or continue intrathecal therapy, or modify antibiotic selection after identifying the pathogen and carrying out quantitative disc sensitivity tests.

McCracken[20] has recently summarized a revealing experience with bacterial meningitis in newborn and young infants. His observations in Dallas spanned 1966 to 1971 and included 38 infants, 21 percent of whom were preterm infants. The mortality rate was low, 19 percent, but the morbidity data were very provocative, relating quite clearly to the type of pathogen and the immediate therapeutic response. Antimicrobial treatment consisted of parenteral administration of ampicillin or penicillin combined with kanamycin or gentamicin. Almost a third of the patients were also treated with intrathecal or intraventricular administration of polymyxin B, kanamycin or gentamicin. Gram-positive pathogens, largely group B streptococci, were promptly eradicated from the spinal fluid and 50 percent of the infants so treated were neurologically normal at 2 to 3 years of age. Gram-negative pathogens, primarily Escherichia coli and Klebsiella species, were very slowly cleared from the spinal fluid, the organisms persisting in the spinal fluid for as long as one week, and only 10 percent of these infants were free of neurologic sequelae at 2 to 3 years of age.

Other speculative but untested components of therapy include gamma globulin, a source of IgG opsonins, and fresh adult whole blood transfusion which provides more suitable levels of erythrocyte 2, 3-diphosphoglycerate plus IgM lytic opsonins and complement. Doppler techniques and intra-aortic direct measurement of blood pressure offer superior methods for the detection of shock in perinatal and neonatal infection. The supplementation of routine antibiotic therapy with the physiologic control of shock, acidosis and hypoglycemia may offer the ultimate solution for not only the residual mortality but also the intractable, serious neurologic morbidity. Colloid, isoproterenol and enormous vasoactive doses of hydrocortisone should be explored more vigorously for their contribution to the management of these serious infections. Sodium bicarbonate and parenteral administration of glucose are standard therapeutic modalities in infant special care units and must be considered in the management of infectious illness also.[76,77]

Disseminated intravascular coagulation occasionally complicates infection in young infants and intravenous heparin may offer helpful treatment—although the titration of anticoagulation may be delicate. The use of heparinized whole blood for other purposes as discussed above may also suffice to control moderate intravascular coagulopathy. Intravascular coagulopathy can be distinguished from the hemorrhagic disorder of profound hepatic dysfunction by the assay of factor VIII (AHG), which is decreased with intravascular coagulopathy and normal with liver disease.

Staphylococcal infection, more commonly now Ritter's disease produced by phage type 71 organisms, may be treated with uniform success with parenteral methicillin. As mentioned above, we have found amphotericin therapy of systemic candidal infection, including occasional intrathecal treatment, to be successful and free of therapeutic

complications.[40] We have gained some experience with parenteral and intrathecal treatment of systemic perinatal herpes simplex type 2 virus infection with cytosine arabinoside.[78] Infants have survived with and without such therapy and so we can draw no conclusion regarding the efficacy of systemic antiviral chemotherapy. Frankly, with a few exceptions, the experience throughout the country does not offer a great deal of optimism concerning chemotherapy of perinatal herpes simplex virus or cytomegalovirus infection with cytosine arabinoside, adenine arabinoside and 5-fluoro or 5-iodo-2-deoxyruidine.[79-84]

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Orthopedic Applications of Liquid Crystal Thermography

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Liquid crystal thermography can assist the clinician in evaluating inflammatory conditions or delineating viability of tissues by the differences in coloration that occur with the use of these unique substances. The technique has proved useful in studying hemophilia, tumors of the extremities, arthritis and vascular conditions, including the complications of diabetes.

THE VARIOUS clinical and physical properties of liquid cholesteric crystals have been known since the turn of the century. More recently advantage has been taken of these properties to study various subsurface conditions, particularly with regard to aerodynamic and electronic structures.[1] It has only been in the last ten years that the medical applications of liquid crystal thermography have been explored.[2,3] The clinical application of liquid crystals in medicine involves skin application to define relative temperatures which are modified by underlying conditions.

Some cholesterol ester derivatives in the liquid crystal form are highly sensitive to variations in skin temperature which they convert almost instantaneously into reversible color values. Cholesteric liquid crystals are organic compounds which exhibit mechanical properties of liquids and optical properties of solids. The substance is unique in that the molecule is neither in a three dimensional array as in a solid nor in a free form as in a liquid. Instead, cholesteric liquid crystals form layers which are free to slide over one another or revolve around a fixed axis. This property is responsible for the color changes associated with differentials in temperature to the areas on which they are applied. Normally the liquid is colorless, but the molecules realign themselves in response to temperatures of adjacent substances.[4] The colors that are produced are the reverse of the conventional color scheme associated with heat. The spectrum of colors produced from these substances begins with red at the cool end of the spectrum and progresses through green to deep blue for the warm end of the scale. The underlying base coat of black is visible when the recorded temperature is beyond either end of the temperature scale.

We have used the technique discussed in this paper to study various orthopedic conditions including spina bifida, various types of tumors,

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hemophilia,[5] arthritis and various other inflammatory and vascular conditions. In addition, we have used this technique to objectively assess the benefits of treatment rendered for intra-articular inflammatory disease.

Materials and Methods

The technique of application begins with obtaining a black background before the cholesteric crystals are applied. This can be accomplished either by applying a plastic sheet, such as the Vidrape that is used in surgery, that has been painted black, or by direct application of a black paint to the area to be investigated. The clear liquid cholesteric crystal solution is then sprayed on the area. Because the crystals are affected by subsurface temperature, variations in color appear.[6] The area investigated is then photographed. A 35 mm single reflex camera is used, Ektachrome-x® is the preferred film. The camera is equipped with a rotating polarizing filter. Strobe light being a cool light is the most suitable light source. The flash unit, too, must be equipped with a polarizing filter, eliminating the reflections of the fatty cholesteric liquid crystals. The photographs are analyzed for areas of relative temperature differential. In the evaluation of joint disease, a baseline study is carried out and then follow-up studies are conducted at timely intervals to evaluate the effectiveness of the treatment program.

Clinical Uses

In symptomatic but clinically undefined cases, liquid crystals may help to determine the site of inflammatory lesions. A common example is a patient with complaint of pain yet in whom no clinical signs of tissue disorder are found. In such cases the lesion can be localized and an estimate of the extent of the lesion, which may be inflammatory, traumatic, degenerative, infectious or neoplastic in origin, can be defined. The extent of inflammation from a synovitis is readily apparent through this technique. It is also a useful diagnostic aid in examining infants with myelodysplasia where sensory responses are unreliable yet skin temperature changes secondary to the paralysis are easily defined. The specific level of involvement can thus be objectively delineated and formulation of a treatment plan at a very early stage of disease is possible. Peripheral vascular disease is frequently more clearly defined with this technique, for example, the level of gangrenous changes in diabetes mellitus or in occlusive disease can be estimated.

Reports of Cases

We have found the technique to be of use not only in diagnostic procedures but also in objectively following the results of treatment. The following represent several illustrative case reports.

Case 1. This case is that of a patient with bilateral plantar fasciitis. Clinically the patient had tender heels, more so on the left side than on the right, and walked with some difficulty. Calcaneal spurs bilaterally were seen on x-ray films. Figure 1a shows a preinjection thermogram, the blue area representing the area of the inflamed attachment of the plantar fascia to the os calcis. The symptomatic side, the left side, was injected with a combination of 1 percent solution of lidocaine and a cortisone derivative. The second thermogram (Figure 1b) was taken three days after the injection and shows the change in hue which indicates decreasing underlying temperature and which correlated with the resolving of the inflammatory condition. This therapeutic benefit continued until approximately 26 days following initial injection. These thermographic findings correlated with the clinical response.

Case 2. A patient was seen with juvenile rheumatoid arthritis with severe involvement of all joints, particularly the small joints of the hand. The most involved joint was the metacarpophalangeal joint in the index finger of the left hand and this corresponded with the blue area on the initial thermogram (Figure 2a). An intra-articular injection of steroid and lidocaine was administered and serial thermograms made. Progression of thermographic change in color corresponded with clinical improvement throughout the course of follow-up which in this instance was six weeks (Figure 2b).

Case 3. A patient with juvenile rheumatoid disease involving primarily the knees was seen. The patient previously had synovectomy carried out on the left knee and at the time of thermography was known to be symptomatic in the right knee. The unoperated right side was injected with an intra-articular steroid and lidocaine combination and serial thermograms were made (Figures 3a and 3b). Return of the blue color corresponded with recurrence of symptoms after a symptom-free period of approximately three weeks.

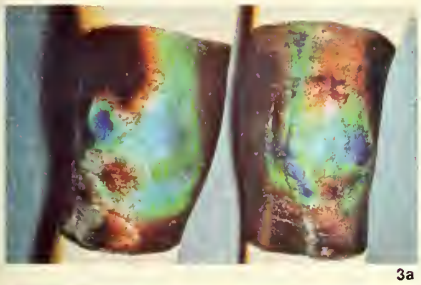
Case 4. This patient, with classic hemophilia-A, presented with multiple joint hemorrhages par-

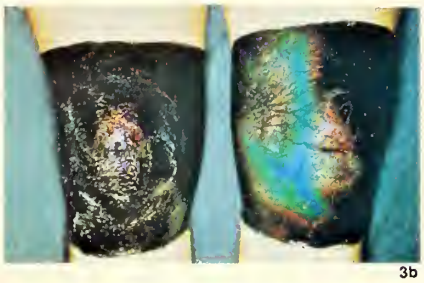
1a

1b

2a

2b


3a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4a

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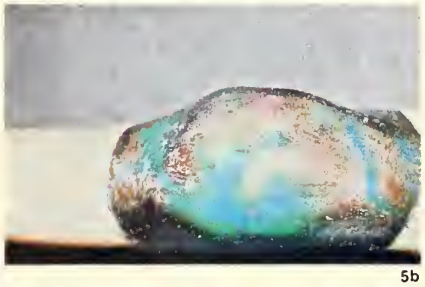
5a


5b

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upper, 10a; lower, 10b

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13

ticularly in the left hand, as indicated by preconcentrate thermograms (Figure 4a). The patient was given plasma concentrate and thermograms were made again after ten minutes (Figure 4b). The change in color correlated with the clinical improvement and was consistent with the cessation of bleeding into the localized areas, and the resolving "hot spots" in the joints of the hands.

CASE 5. This case is that of another patient with classic hemophilia-A, this one presenting with acute hemarthrosis of the knee. Figure 5a shows a thermogram of the involved knee before treatment. Figure 5b shows one made 20 minutes after plasma was given. A striking difference in color and also in the clinical appearance of the joints can be seen.

Liquid Crystals and Delineating the Extent of Various Orthopedic Conditions

It should be stated at the outset that the diagnosis of an actual condition is not made using this technique; however, it is a valuable adjunct in determining and delineating the extent of the pathology to be encountered.[8] Beginning with myelodysplasia, it is particularly of use when one considers the difficulty in assessing a sensory level in neurologic deficit in a newborn infant. A good example is seen in Figure 6 where the set-up point is in the midline below the level of the iliac crest and in the superior portion of the gluteal cleft. Again on another patient, one can see the black background on the extremity which indicates that the area is out of the temperature range tested compared to that more proximal area in the trunk where the blue coloration indicates warmer temperature, Figure 7, thus giving an indication of the level of the lesion.

This technique is also applicable, as previously mentioned, to vascular conditions. In this regard, Figure 8 shows thermograms of a patient's right and left legs. The blue-green color of the uninvolved left leg is to be compared with the black to orange colors in the right lower extremity, which was pulseless. A second example of vascular disease (Figure 9) is that of a patient with Raynaud's disease. A differential in circulation can be seen in the patient's fingers.

Crystal thermography can also be used to determine the presence and extent of various tumors. An example is a patient we saw with a cavernous hemangioma of the right hand. In the plain photograph (Figure 10a) one can see the bluish discoloration in the right palm. A thermogram (Figure 10b) shows the much larger extent of this tumor than one might previously have anticipated on the basis of the clinical appearance. A second example is that of a young patient seen with undifferentiated sarcoma of the right side. The obvious area of increased temperature is noted on the thermogram (Figure 11). A third example is that of a patient who presented with vague joint pain in the right knee. No abnormalities were noted on x-ray studies. A temperature differential between the two knees was seen on thermograms (Figure 12) and subsequent microscopic diagnosis of the lesion in question showed synovial sarcoma. Another patient presented with a tender area in the right distal femur noted approximately three months before being seen. Thermography showed the isolated area of increased temperature over a lesion which proved to be an osteochondroma of the distal femur (Figure 13).

Conclusions

Liquid crystal thermography has limited general clinical application. However, the technique has proved to be a relatively simple method of studying various orthopedic conditions and determining the extent of the underlying pathology. It has also proved to be an objective way of evaluating the results of treatment in various inflammatory diseases.

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Refer to: Lewis JE, Mello P, Knauer CM: Isoniazid-associated hepatitis—Serum enzyme determinations and histologic features. West J Med 122:371-376, May 1975

Isoniazid-Associated Hepatitis

Serum Enzyme Determinations and Histologic Features

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A prospective study of 208 patients treated for up to 12 months with isoniazid (INH®) for tuberculosis prophylaxis was made. Levels of serum glutamic oxaloacetic acid transaminase (SGOT) became elevated in 20 percent of the adults followed and in 30 percent predominantly nonspecific symptoms developed, in 11 percent simultaneously with SGOT elevation; SGOT levels became elevated in two of 33 children and 1 was symptomatic. Mild SGOT elevations in asymptomatic adults were self-limited; however, a small percentage of symptomatic adults showed prolonged SGOT elevation for months after INH was completed. Results of liver biopsy studies in the early stages of SGOT elevation generally showed portal and periportal lymphocytic infiltrations with lesser numbers of plasma cells, neutrophils and eosinophils.

DOCUMENTATION OF THE therapeutic and prophylactic effectiveness of isoniazid (INH®) as an antituberculous agent has been well established,[1] as has its toxicity in a variety of organ systems.[2,3] Toxic hepatic injury with fatty degeneration after large doses of INH was shown in dogs in 1952.[4] Hepatitis associated with the administration of INH in the usual doses of 3 to 5 mg per kg of body weight per day in adults not also receiving para-aminosalicylic acid or streptomycin or both has recently been documented.[5-16]

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Five patients with INH-associated hepatitis were studied at Santa Clara Valley Medical Center from September 1970 through October 1971.[5] These cases in addition to other reports of INH-associated hepatitis[6,7] led us to initiate a prospective study to evaluate the frequency and severity of physiologic, histologic and symptomatic features of hepatitis and the possible role of associated medical conditions in patients prophylactically receiving INH.

Methods

Isoniazid therapy (3 to 5 mg per kg of body weight per day given orally) was begun in all patients seen in the Tuberculosis Clinic of the Santa Clara County Health Department between October 1971 and March 1972 who met the following

ABBREVIATIONS USED IN TEXT

HAA® = hepatitis-associated antigen
INH = isoniazid
SGOT = serum glutamic oxaloacetic transaminase
SGPT = glutamic pyruvic transaminase

criteria for chemoprophylaxis with INH: (1) recent conversion of tuberculin skin test results from negative to positive or (2) positive tuberculin test and recent contact with tuberculosis patients deemed infectious. No patient was excluded because of any underlying medical illness—including diabetes mellitus, obesity, history of liver disease, seizure disorders, pregnancy and alcohol abuse. General clinical evaluation, a tuberculin skin test, a roentgenogram of the chest and a baseline serum glutamic oxaloacetic transaminase (SGOT) measurement done before institution of INH therapy were required before inclusion in the study. Clinical evaluation and SGOT determination were repeated 1, 2, 3, 6, 9 and 12 months subsequently. If an SGOT level became elevated, serum bilirubin, alkaline phosphatase, glutamic pyruvic transaminase (SGPT) and hepatitis-associated antigen (HAA) were also measured simultaneously. Liver biopsies were done on the first eight patients in whom results were abnormal for two or more consecutive SGOT measurements, and on one additional patient in whom there were sustained SGOT elevations for a year after completion of therapy.

All patients were treated for one year. Patients who had at least two measurements of SGOT levels obtained within the first four months of therapy plus at least two levels during the subsequent eight months were considered to have had adequate one year follow-up. Isoniazid was discontinued when overt clinical hepatitis developed as well as when clinical evidence of toxicity to other organ systems occurred.

Results

Of the 208 patients treated with INH, ranging from 1 to 70 years of age, 19 were excluded from the study because of inadequate evaluation. Of the remaining 189 (156 adults and 33 children), 118 (63 percent) were followed for the full 12 months of INH therapy or until elevated SGOT levels returned to the normal range after discontinuation of INH. In the remaining 71 patients, at least two measurements of SGOT levels were obtained during the first four months but the minimum number required for adequate one year follow-up was not obtained. Clinical signs and symptoms of hepatitis were generally nonspecific (Table 1). Elevation of SGOT occurred in 20 (43 percent) of the 47 symptomatic adults, in 17 (16 percent) of the 109 asymptomatic patients and in 25 (18 percent) of the 142 patients without history of alcohol abuse.

Adults

Elevated SGOT levels before INH therapy: Six patients had elevated SGOT levels before initiation of INH therapy (Table 2). Two were known alcohol abusers and had mildly elevated serum bilirubin levels before treatment; SGOT levels remained elevated in one for 13 weeks of INH therapy—at which time the patient was lost to follow-up—and in the other patient, they returned to and remained within normal limits during INH therapy. One patient in whom a slightly elevated pretreatment level of SGOT was noted was a 19-year-old woman with a history of hepatitis who was on oral contraceptive therapy; the level returned to and remained within normal limits during INH therapy. In one 34-year-old woman (case 1, addendum) who was on oral contraceptive therapy, SGOT levels remained mildly elevated until week 22 of INH administration—at which time icterus and other symptoms of INH-associated hepatitis developed. The remaining two had no pertinent medical history to account for the enzyme elevations; the SGOT level returned to the normal range during 12 months of INH therapy in one and fluctuated but became normal by completion of therapy in the other.

Transient SGOT elevation during INH therapy:

TABLE 1.—*Signs and Symptoms in 156 Adults Receiving Isoniazid (INH®)*

*Symptoms**	*Number of Patients*	*Percent*
Headache	13	8.4
Myalgias	12	7.7
Malaise-fatigue	11	7.0
Abdominal discomfort	9	5.8
"Dark urine"	8	5.1
Nausea	7	4.5
Hepatomegaly	7	4.5
Arthralgias	6	3.8
Dizziness	6	3.8
Rash	6	3.8
Anorexia	5	3.2
TOTAL	47	30.0

*The following symptoms were noted in <3 percent of the patients: diaphoresis, pruritus, vomiting, visual abnormalities, diarrhea, dysesthias, irritability, fever and icterus (one patient).

TABLE 2.—*Summary of INH-treated Patients with SGOT Elevation*

	Sustained SGOT elevations (19 patients)	*Transient SGOT elevations (12 patients)*	*Pre-INH SGOT elevations (6 patients)*
Weeks of INH before elevation	3 to 40 weeks	2 to 33 weeks	
Peak SGOT (R-F units)*	47 to 179 units	44 to 84 units	65 to 282 units
Premature INH discontinuation	5 patients	1 patient	2 patients
Failure of SGOT to return to normal levels	6 patients: 4 with early elevations were lost to follow-up while levels still elevated; in 1 still elevated 5 months after INH completed; in 1 still elevated 1 year after INH completed—amyloid on liver biopsy. Returned to normal in 6 patients at or shortly after completion of INH	All normal by the end of 1 year of INH	In 1 elevations maintained through 13 weeks when lost to follow-up; 1 only after icterus led to INH discontinuation at 22 weeks

*Reitman-Frankel Units, normal less than 40 units.[17]
INH® = isoniazid.
SGOT = serum glutamic oxaloacetic acid transaminase

TABLE 3.—*Frequency of SGOT Elevations in Subgroups According to Underlying Medical Condition**

Subgroups	*Affected Number*	*Total Number Patients*	*Percent with SGOT Elevation*
Pregnancy	0	6	0
Diabetes	3	12	25
Previous hepatitis	1	4	25
Obesity	10	33	30
Alcohol abusers	7	14	50

*A single patient may have had one or more of the underlying medical conditions; however, there was no overlap in the patients with previous hepatitis.

Twelve patients with normal pretreatment SGOT levels had single or nonconsecutive elevations of SGOT during therapy (Table 2). In the ten with a single SGOT elevation, the abnormal level occurred between weeks 5 and 13 in six and between weeks 27 and 33 in four. The nonconsecutive elevations in the two patients occurred from weeks 2 to 16. Three of the 12 were alcohol abusers: in one, dark urine occurred at five weeks but serum bilirubin, alkaline phosphatase and SGPT levels were normal and HAA was negative; in the second, there were tender hepatomegaly, spider angiomata and an elevation of SGOT, SGPT and alkaline phosphatase and normal bilirubin at eight weeks, and in the third, SGOT was slightly elevated on one occasion.

In one patient in whom there were nonconsecutive SGOT elevations, headaches, arthralgia, myalgias, an SGOT level of 68 units and mildly elevated alkaline phosphatase occurred two weeks after starting INH; INH was discontinued for three days and then reinstituted at 2 mg per kg of body weight per day temporarily before returning to the previous dosage. The SGOT returned to normal levels except for a single mild elevation at 12 weeks. The patient was able to complete 12 months of INH therapy without further complication.

Persistent SGOT elevation during INH therapy: In 19 patients in whom pretreatment SGOT levels were normal, there were two or more consecutive SGOT elevations, 18 within 3 to 20 weeks of therapy and one at 40 weeks. Of 11 patients in whom SGPT was measured, eight had SGPT levels higher than the SGOT measurement. Alkaline phosphatase and bilirubin were usually within normal limits. In all 16 patients tested, HAA was negative.

Percutaneous liver biopsy was done in eight patients. In five, nonspecific hepatitis was evidenced by varying degrees of portal and lobular infiltration with predominant lymphocytes but with some plasma cells, neutrophils and eosinophils. Slight portal fibrosis and early bile duct proliferation were found in another patient (Case 2, addendum), and pronounced macrovesicular and mild microvesicular fatty metamorphosis were noted in the liver of a slender patient without history of alcohol abuse in whom there had been persistent elevation of SGOT for five months after completion of a year of INH therapy. In the eighth patient (Case 3, addendum), SGOT levels increased to 52 units at five weeks and to 68 units at nine weeks of INH therapy, and continued to remain mildly elevated for a year after completion of 12 months of INH. Results of liver biopsy a year after completion of INH therapy showed

amyloidosis, moderate fatty metamorphosis and mild fibrosis.

Subgroup analysis: Subgroups of adult patients according to pregnancy, diabetes mellitus, previous hepatitis, obesity and alcohol abuse were analyzed (Table 3).

Children

In the INH-treated children, SGOT abnormalities developed in two of the 33. In one, the increase was associated with an allergic diathesis, and in the other the level increased to 57 units just before completion of 12 months of INH therapy but returned to the normal range one month later.

Discussion

Three prospective studies on the hepatic abnormalities associated with INH chemoprophylaxis (Table 4) have been reported since 1969.[6,13,14] In the largest series,[14] neither SGOT nor other liver function tests were done until most patients had received INH for five to eight months, whereas in our series and those of others,[6,13] elevations appeared much earlier. The ranges and peaks of SGOT elevations did not vary significantly in the four studies.

Of the 156 adults in our series, SGOT elevations and symptoms of hepatitis were noted in 11 percent and these were considered to have INH-associated hepatitis. This incidence is higher than those of other studies[6,13,14] and may partially reflect our heterogeneous population in which no attempt was made to exclude patients with underlying medical illnesses.

The symptoms seen in patients receiving INH were mostly nonspecific. Abdominal discomfort, vomiting and dizziness were as common in patients with normal SGOT levels as in those with elevated SGOT levels, suggesting that they were pharmacologic side-effects of INH therapy. The presence of rash, fever and eosinophilia suggests a hypersensitivity (immunologic) response, which may play a role in the mechanisms of INH-associated hepatitis.[3,8,9,18] Overt signs of hepatitis were usually late manifestations of INH-associated hepatitis in our patients. Although anicteric viral hepatitis cannot be excluded in any of the patients, the temporal relationship with the initiation of INH therapy, the negative HAA, the lack of known exposure to hepatitis, and the return of SGOT levels to normal values after discontinuation of INH strongly implicate this drug as the causative agent.

TABLE 4.—*Comparative Data in Prospective INH Chemoprophylactic Studies*

	Scharer et al[8]	*Byrd et al*[13]	*Bailey et al*[14]	*Lewis et al*
Number of patients	90 patients	160 patients	427 patients*	189 patients
Population	Hospital employees (New York)	Military personnel (Illinois, Colorado and Maryland)	Hospital employees (Louisiana)	Tuberculosis Clinic (Santa Clara County, California)
Age of patients (yr)	Adults (average 39)	Adults (average 36 males; 38 females)	Adults (range 19-65)	156 adults (average 39 males; 35 females) 33 children (average 8.3)
Total no. of patients with SGOT elevations	11 (12.2%)	42 (26.2%)	37 (8.7%)	32 (20.6%)† 2 (6.1%)
Symptomatic	2 (2.2%)	9 (5.6%)	5 (1.2%)	18 (11.5%)† 1 (3%)
Asymptomatic	9 (10%)	37 (20.6%)	32 (7.5%)	14 (9.4%) 1 (3%)
SGOT range	65 to 160 R-F units	50 to 1,400 units	50 to 940 mμ/ml	44 to 282 R-F units 57 to 61 R-F units
Jaundice present	0	0	3	1 0
Liver biopsies described	1	0	2	9 0
Total no. of cases of INH discontinuance	2 (2.2%)	16 (10%)	18 (4.2%)	13 (8.7%) (5 medically) 4 (12%) (1 medically)
Pre-INH SGOT measured	Yes	Yes	No	Yes Yes
Frequency of SGOT sampling	Weekly	1, 3, 6, 9 and 12 months	None until monthly sampling after 5-8 months INH	1, 2, 3, 6, 9 and 12 months 1, 2, 3, 6, 9 and 12 months

*Early months data missing.
†Includes 1 patient with elevated pretreatment SGOT who progressed to icterus at 22 weeks (Case 1, addendum).

INH=isoniazid.
SGOT=serum glutamic oxaloacetic acid transaminase
R-F units=Reitman-Frankel units

A variety of histopathologic lesions have previously been reported in INH-associated hepatitis including noncaseating granulomata,[5] cholestasis,[5,16] bridging necrosis,[18] fibrosis,[14] chronic active hepatitis[14] and massive hepatic necrosis[14,15]—as well as the more typical hepatocellular changes resembling viral hepatitis[5,6,8,11,15,19] seen in most of our patients in whom biopsies were done. Most liver biopsies in our series were done early in the course of treatment when SGOT elevations were not as high; peak SGOT levels occurred 2 to 21 weeks after the biopsies were done in five of the six patients in whom INH therapy was continued.

Conclusions

Thirty percent of the 156 adults treated with INH were symptomatic. Eleven percent had concomitant SGOT elevations and were considered to have INH-associated hepatitis. Of the adults with SGOT elevations and no symptoms of hepatitis (9 percent), three in whom liver biopsy studies were done had histologic abnormalities. In the absence of other obvious causes, patients in this group probably had subclinical INH-associated hepatitis. Mild SGOT elevations in asymptomatic patients were self-limited.

When symptoms are present, SGPT may be a more sensitive indicator of INH-associated hepatitis than SGOT, with bilirubin and alkaline phosphatase frequently remaining normal until late in the course of the disease. In a small percentage of the symptomatic patients, there were prolonged elevations of SGOT levels even after discontinuance of INH therapy that were still elevated in some at the end of follow-up (one year).

Because of these findings, we recommend that monthly clinical evaluations be made in patients receiving INH. In symptomatic patients, liver function tests to include SGOT, SGPT, bilirubin, alkaline phosphatase and HAA should be done and in those with prolonged elevation of hepatic enzymes, or elevated bilirubin or alkaline phosphatase, INH administration should be discontinued. Liver biopsy may be indicated in this group particularly if the results of liver function tests do not return to normal values after INH is discontinued.

Addendum: Selected Case Histories

CASE 1. A slightly obese 34-year-old woman reported transient cough and myalgias one month before visiting the Tuberculosis Clinic in January 1972. On chest roentgenogram, no abnormalities were noted; SGOT and SGPT were 58 and 84 units, respectively, with normal bilirubin and alkaline phosphatase levels and no history of liver disease or alcohol abuse. Oral contraceptive pills and diphenhyramine hydrochloride (Benadryl®) were the only medications being taken by the patient. Treatment with INH was begun. Two weeks later, anorexia and nausea occurred. Administration of INH was discontinued and when symptoms resolved three days later, it was resumed at the same dosage. During week five the patient was asymptomatic, HAA was negative but SGOT level was 65 units, SGPT 42 units and results of liver biopsy showed pronounced macrovesicular fatty metamorphosis, patchy microvesicular fat as well as focal portal and periportal necrosis with lymphocytes, plasma cells and some eosinophils. Because there were no symptoms of INH toxicity at this time, INH was continued. During week 22, anorexia, fatigue, dark urine, acholic stools, scleral icterus and tender hepatomegaly developed; SGOT was 282 units, total bilirubin 6.2 mg per 100 ml, alkaline phosphatase 4.6 Bodansky units (normal 1 to 4.5) and HAA negative. Isoniazid was discontinued and the signs and symptoms gradually subsided; SGOT was 65 units eight weeks after cessation of INH therapy and within normal limits 20 weeks after cessation.

CASE 2. A 53-year-old chronic alcohol abuser with a history of emphysema was seen in the Tuberculosis Clinic in December 1971 because of positive findings on a tuberculin skin test. Aortoiliac endarterectomy for claudication had been done in July 1971. The SGOT levels measured in October and December 1971 before INH therapy were within normal limits. Two weeks after starting INH, bilateral ankle pain developed and progressed to ischemic changes in the feet, a temperature of 38.3°C (101°F) developed and the patient was admitted to the hospital. On roentgenograms of the chest, bilateral perihilar pneumonitis was noted, although sputa grew normal flora. Leukocyte count was 20,000 per cu mm with a left shift, SGOT 132 units, total bilirubin 2.2 mg per 100 ml, alkaline phosphatase 66 King Armstrong units (normal <17), creatinine 2.1 mg per 100 ml and prothrombin time 60 percent of normal activity. Isoniazid was discontinued and parenteral penicillin, 600,000 units every six hours for seven days, and oral tetracycline, 500 mg every six hours for four days, were administered.

Findings on percutaneous liver biopsy on day seven showed increased portal connective tissue,

mild chronic inflammatory infiltrate and early bile duct proliferation. The pneumonitis cleared. Results of liver function tests were within normal limits one month after admission to hospital.

CASE 3. A 65-year-old slightly obese man was seen in the Tuberculosis Clinic in March 1972 because of positive response to a tuberculin skin test. He reported a history of drinking a glass of wine with dinner until INH therapy was begun. The level of SGOT, which was within normal limits before INH, increased to 52 units by week five and continued to increase to twice normal values during the year of treatment. The only symptoms were mild chills and sweats during the first few months of therapy. During the year after discontinuance of INH, SGOT and SGPT levels remained approximately twice normal, and findings on liver biopsy included amyloidosis, moderate fatty metamorphosis, mild bile duct stasis and mild fibrosis. On complete blood cell count, no abnormalities were noted except for slight erythrocytic macrocytosis and rare target cells. Mild lymphocytosis and plasmacytosis were noted on bone marrow biopsy specimens, and cultures for acid-fast bacilli were negative. Urine was negative for Bence-Jones protein. Serum bilirubin and alkaline phosphatase levels and protein electrophoretic values were normal. Rheumatoid arthritis titer was negative. Prothrombin time was 60 percent of normal activity.

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The Consequences of Habitual Knuckle Cracking

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Habitual knuckle cracking in children has been considered a cause of arthritis. A survey of a geriatric patient population with a history of knuckle cracking failed to show a correlation between knuckle cracking and degenerative changes of the metacarpal phalangeal joints.

MANIPULATING THE metacarpal-phalangeal (MCP) joints and sometimes the proximal interphalangeal (PIP) joints in such a manner as to produce an audible popping or cracking sound is a commonly observed childhood habit not infrequently persisting into adult life. Unsworth, Dowson and Wright have recently shown that the cracking sound can be explained by a collapse of synovial fluid vapor cavities that result from the negative pressure induced by MCP joint distraction.[1] Although knuckle cracking (KC) appears to cause some comfort or satisfaction to the person doing it, the apparent traumatic component dramatized by the popping sound suggests to many people that joint disorders and specifically arthritis would be an inevitable outcome.[1] As a consequence, many children with this habit are chided to stop cracking their knuckles lest arthritis or enlarged knuckles or both develop. In light of the relative rarity of MCP osteoarthritis and in view of the apparently common prevalency of habitual knuckle cracking it was decided that a correlation of MCP osteoarthritic changes in a geriatric population with a history of KC would be of interest.[2-7]

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Materials and Methods

Twenty-eight patients (residents of a Jewish home for the aged) who were able to recall whether or not they cracked knuckles (and in the case of a positive response were able to demonstrate a KC maneuver) were examined clinically and by x-ray. Traumatic arthritis other than that which might be associated with KC, rheumatoid arthritis, gout, chondrocalcinosis and hemachromatosis cases were excluded. Standard anteroposterior radiographs of the hands were studied. The patient population consisted of 28 persons, with an average age of 78.5 years, of whom 23 were women and 5 were men. The patients were unselected except for their ability to clearly recall whether or not they had been knuckle crackers and their agreement to have an x-ray study of the hands done for the purposes of this study. A population of 28 school children at a summer camp, with an average age of 11 years, consisting of 8

ABBREVIATIONS USED IN TEXT
DIP = distal interphalangeal
DJD = degenerative joint disease
KC = knuckle cracking
MCP = metacarpal-phalangeal
PIP = proximal interphalangeal

girls and 20 boys was surveyed in an effort to assess the prevalence of KC in a younger population group.

Results

For the purposes of this study which was designed to detect bony enlargement and degenerative arthritis in the MCP joints, radiographically identifiable osteophytes were required for the diagnosis of MCP degenerative joint disease (DJD). Only one patient with a history of KC showed MCP DJD compared with 14 knuckle crackers who showed no changes (see Table 1). MCP osteophytes were observed in five patients who had no history of KC. Eight additional patients who were not knuckle crackers had normal MCP joints. Analysis of the data reveals a negative correlation between KC and MCP DJD in the geriatric population studied (P = 0.06). Further analysis of this population group for possible sex bias indicated that of the women patients studied, one of 11 KC positive women had MCP DJD while five of 12 KC negative women had MCP DJD. There was a lack of a positive correlation of KC in the women with MCP DJD (P = 0.10). Four of the five men gave a history of KC, but MCP DJD was not noted in any of them.

Table 2 indicates the correlation of KC prevalence in two age populations. The data suggest that the prevalence of KC in geriatric men was not different from that of the 11-year-old boys (P = 0.14) and that the same observations appear to be applicable to the females with a lesser degree of certainty indicated by a P value of 0.24.

Table 3 shows that when radiographic correlations of the MCP DJD with proximal interphalangeal (PIP) DJD were made, PIP DJD was present in all six of the cases with demonstrable MCP DJD. Only eight of the 13 cases without MCP DJD had PIP DJD. There was therefore a high correlation of MCP DJD with PIP DJD (P = 0.01). Additionally, in five of the six patients with PIP osteophytes, typical distal interphalangeal (DIP) osteophytes were seen on the anteroposterior roentgenograms of the hands.

TABLE 1.—*Correlation of Knuckle Cracking (KC) with Metacarpal-Phalangeal (MCP) Degenerative Joint Disease (DJD)* in a Geriatric Population (Average Age 78.5 Years)*

	KC Yes (+)	*KC No (−)*	*Total*
MCP DJD(+)	1	5	6
MCP DJD(−)	14	8	22
TOTAL	15	13	28

*DJD for the purpose of this study is defined as a roentgenographically identifiable osteophyte on a standard anteroposterior view.

TABLE 2.—*Correlation of Knuckle Cracking (KC) Prevalence in Two Age Groups*

	Female Average Age		*Male Average Age*	
	81.4	*11*	*76.0*	*11*
KC Yes(+)	11	2	4	8
KC No(−)	12	6	1	12
TOTAL	23	8	5	20

TABLE 3.—*Correlation of Metacarpal-Phalangeal (MCP) Degenerative Joint Disease (DJD) and Proximal Interphalangeal (PIP) DJD*

PIP DJD	*MCP DJD Present*	*MCP DJD Absent*
Present	6	8
Absent	0	13

All six cases with MCP DJD had PIP DJD, but only 8 of 13 cases without MCP DJD had PIP DJD. MCP DJD correlates with PIP DJD (P = .01). Five out of six patients with PIP osteophytes had typical distal interphalangeal (DIP) osteophytes on the A-P hand roentgenograms.

Discussion

Analysis of the prevalence of KC in the geriatric population when compared with a group of 11-year-old youngsters suggests that the prevalence of KC in the geriatric population that was studied was not significantly different from what one observes in a youthful population susceptible to habitual quirks and mannerisms. The proportionately greater prevalence of KC in the geriatric patients apparently reflects a selection factor inherent in the study design. Only those geriatric patients who could recall specifically if they did or did not crack their knuckles were entered into the study. Although no records were kept, a considerable number of patients in this age population were unable to remember with certainty whether or not they cracked their knuckles. It seems likely that those geriatric patients who did not crack their knuckles in childhood would have more uncertainty when questioned and the bias of patient

selection would be to include a higher proportion of knuckle crackers.

The failure to positively correlate degenerative changes in the MCP joints in the patients who described habitual KC was of great interest. The observation that in all of the patients with MCP DJD, whether or not they were knuckle crackers, there was radiographic evidence of PIP DJD and in five of those six there was radiographically demonstrable DIP osteoarthritis on standard anteroposterior views of the hands (in all six of these patients, Heberden's nodes were present clinically) strongly suggests that MCP DJD is a function of whatever the predisposing factors are to osteoarthritis involving the distal interphalangeal and proximal interphalangeal joints and that MCP DJD is not a consequence of knuckle cracking.

Conclusion

The data fail to support evidence that knuckle cracking leads to degenerative changes in the metacarpal phalangeal joints in old age. The chief morbid consequence of knuckle cracking would appear to be its annoying effect on the observer.

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Persistent or Slow Viral Infections and Related Diseases

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The discovery of persistent transmissible agents by veterinarians has led to striking advances in the infectious cause of neuropathies of human beings. There is evidence for persisting infection in congenital rubella and the herpes group of viruses including cytomegalovirus infections. Hepatitis types A and B are candidates for inclusion in the category of persisting viral infections.

The rubeola or measles virus is established as a persistent virus which causes elevated antibodies in the serum and cerebrospinal fluid of many patients with severe demyelinating disease such as subacute sclerosing panencephalitis and multiple sclerosis. Elevated antibodies against vaccinia virus have been found in the cerebrospinal fluid of some patients with multiple sclerosis and neuromyelitis optica, a rare form of multiple sclerosis.

BOTH THE CONCEPT and the reality of slow virus infections was first brought to the attention of the scientific community by Sigurdsson,[1] who successfully isolated viral agents from Icelandic sheep afflicted with a progressive degenerative disease of the nervous system. He defined a slow virus infection as, "an infection of the host in which the agent continued to multiply, slowly producing progressive abnormality over the course of months and years, usually with a very long incubation period, and often with a localization of the infectious process to a single organ." The concept elaborated by Sigurdsson was a relatively strange one to biologists concerned with human diseases. However, it was recognized that rabies may have a long incubation period followed by an overwhelming and fatal illness; lymphocytic choriomeningitis and viral hepatitis also seem to persist causing subacute disease.

Studies by Hotchin[2] on lymphocytic choriomeningitis (LCM) virus infection in mice showed that animals which had been inoculated at birth could suffer from a long continued infection despite high titers of virus. This persistent tolerant infection (PTI) leads, after approximately ten months, to a debilitating fatal disease; in the infected mice the situation is unique in that the LCM virus infection is continuously active at a high level during the life span of the infected animal. In ordinary latency, the level of virus in the in-

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ABBREVIATIONS USED IN TEXT

ALS = amyotrophic lateral sclerosis
CNS = central nervous system
CSF = cerebral spinal fluid
EBV = Epstein-Barr virus
HAA = hepatitis associated antigen
HB = hepatitis B antigen
HI = hemagglutination-inhibition (test)
HSV = herpes simplex virus
Ig = immunoglobulin
IH = infectious hepatitis
IM = infectious mononucleosis
LCM = lymphocytic choriomeningitis
ME = measles encephalitis
MS = multiple sclerosis
NO = neuromyelitis optica
PTI = persistent tolerant infection
SH = serum hepatitis
SSPE = subacute sclerosing panencephalitis
V-Ab = virus antigen-antiviral antibody

fected animal is low or minimal and, indeed, evidence of active virus is often undetectable. In persistent tolerant state, in contrast, virus titer is high, comparable to titers found at the peak of acute viral illness.

PTI also differs in that in PTI infection there is very little antibody. Mice, in which PTI has been induced with certain strains of LCM virus, exhibit a slow virus infection after an incubation period of approximately ten months. After ten months, the mortality rises sharply, reaching approximately 90 percent by 20 months after inoculation, much higher than in control groups. LCM virus is, therefore, an example of a persistent virus disease which results only if the agent is introduced neonatally with consequent production of immunologic tolerance.

Rubella viremia in man might qualify as a persistent tolerant infection since the virus can persist in human infants for 12 to 18 months before the immune system of the infected child is finally able to eliminate it.

The following tentative conclusions have been reached by Hotchin[2] concerning the general properties of slow viruses: (1) they actively multiply to high titers in the host for long periods of time without apparent disease; (2) these viruses are not readily recognized as foreign by the host; (3) an immune reaction to these viral agents is either very late or it does not occur at all; (4) the disease produced may be an autoimmune response caused by termination of tolerance, although the final disease may be a gradual process of erosion of the affected cells by the virus.

Because the host finds great difficulty in recognizing these viruses as foreign, the PTI state is a fundamental prerequisite for slow virus disease. Hotchin's[2] hypothesis of slow virus pathogenesis can be summarized as follows: Slow viruses multiply for a long period of time in the host with access to virtually all types of cells. Infection of certain cell types is followed after a long period by nonmalignant transformation (or other change) of these cells which possibly aided by immune attack, results in loss of function. When the functional reserves are exhausted, clinical disease ensues.

In a recent report Hotchin and associates[3] recorded infection of hospital personnel by lymphocytic choriomeningitis virus, the source of which was shown to be a colony of Syrian hamsters. In persons working with the research colony, acute febrile illnesses developed, some severe. They conclude that the outbreak emphasizes the dangers of working with experimental hamsters. Commercially distributed hamsters have been found to carry LCM virus and have caused human infections. As pointed out previously by Hotchin[2] the LCM virus represents a model for the study of persistent or slow virus infection.

In several chronic viral infections of animals, infectious virus travels in the circulation complexes to host immunoglobulin (Ig), presumably antiviral antibody. According to Oldstone and Dixon[1] virus antigen-antiviral antibody (V-Ab) complexes are competent pathogenic agents and V-Ab immune complex disease probably occurs frequently in chronic viral infections.

The above authors state that, clearly, generalized viral infection with viremia may provide viral antigens which form circulating complexes with host antiviral antibody and complement. They conclude that this form of disease is neither truly a viral nor autoimmune but rather an immune complex disease.

Notkins[5] has proposed the theory that viruses induce immunopathologic lesions by the following mechanism: (1) the virus is a foreign antigen, (2) it is a self-replicating agent and thus can produce a continuous supply of antigen over a long period of time and (3) certain viruses can induce new antigens on the surface of infected cells. These properties may initiate immunopathologic changes through several mechanisms, one of which is to infect the cells of the immune system and thereby produce immunologic derangements.

Studies reported by Notkins[5] showed that herpes simplex virus, vaccinia, influenza and Newcastle disease virus all induced new antigens on the surface of infected cells; the interaction of specific antiviral antibody and complement with these antigens resulted in cell injury. He further suggests that immunological injury may be associated with a variety of acute, recurrent, and persistent viral infections.

Thus, one of the most perplexing aspects of the pathogenesis of persistent virus infections has been the long interval between the initial exposure and the eventual expression of the disease.

Scrapie

Scrapie in sheep (the name refers to compulsive rubbing and scraping against fixed objects) was recognized by farmers in Lincolnshire who petitioned Parliament in 1755 to make it illegal to mix distempered sheep with healthy animals. Affected animals suffer from progressive ataxia, especially in the hind legs, and collapse. Typically, the disease affects sheep at about four years of age and is fatal in a few weeks or months. Sheep which are infected naturally with scrapie virus have an asymptomatic incubation period of three to five years. In the animals infected, there is no febrile phase and there are no changes in cerebrospinal fluid. Lesions are limited to the central nervous system and are concentrated in the cerebellum, where widespread neuronal degeneration and prominent hypertrophy and proliferation of astrocytes are typical (Figure 1). These neuropathological changes differ from those customarily seen in viral infections of the central nervous system.

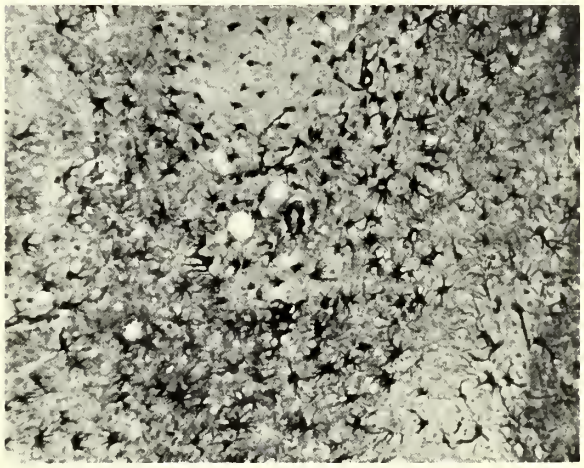

Figure 1.—A photomicrograph of the hippocampus of a scrapie affected rat showing pronounced hypertrophy and proliferation of astrocytes (Cajal reduced from × 200 approx.). (Picture was provided by I. H. Pattison and published by the Journal of the Royal College of Physicians of London, Vol. 1, 93-98, 1966.)

Experimental studies with scrapie have failed to show evidence of an agent-producing disease in primates including chimpanzees. Transmission studies in sheep indicate a very lengthy incubation period extending from four months to four years. However, the passage of scrapie agent to sheep can be continued indefinitely. The agent has been detected in most tissues including brain, spinal cord, pituitary gland, adrenal gland, salivary glands, spleen, liver and lymphatic glands.

The disease is always fatal. Although the agent is filterable and apparently self-replicating, no one has as yet been able to demonstrate it by tissue culture, serology or electron microscopy. Experimental studies with scrapie agent indicate that it has properties that are generally associated with viruses; however, it is remarkably resistant to a number of physical and chemical treatments that destroy conventional viruses.[6] The possibility that it may not contain nucleic acid suggests that a hitherto unrecognized agent may be involved. Its striking similarity to Kuru in man has stimulated great interest in its applicability to other slowly progressive degenerative diseases of unknown cause in both man and animals.

Visna

Visna—a chronic, paralytic and fatal disease of sheep—was the first disease in which Sigurdsson[1] was successful in isolating a persistent virus. The disease is insidious on onset; the earliest symptom is a slight abnormality of gait. The hind limbs become involved and total paralysis gradually occurs. In spite of being unable to rise, the animals live for a considerable length of time after total paralysis, retaining full consciousness. Blindness has been observed in a few cases. The temperature is normal or only slightly increased; the period from onset of first signs of visna to complete paralysis may vary from several months to several years. Remissions are rare and the disease is inevitably fatal.

Lesions in the brain and spinal cord are detectable only by microscopic examination (perivascular infiltration of lymphocytes, profound and widespread demyelination of the white matter around the ventricles, cerebrum and cerebellum, and in the white fibers of the spinal cord).

Sigurdsson[1] transmitted the disease from brains of infected animals and observed that several

months or even years elapsed before any outward signs of illness appeared in the inoculated animals. Signs then developed that were identical with those observed in the natural disease. About one to two months after inoculation but before signs of visna appeared, increased cells were present in the spinal fluid. Cells in the spinal fluid are common in the natural disease and failed to occur in sheep inoculated with normal sheep brain or with other central nervous system diseases. Antibodies developed which were comparable to those found in the natural disease.

In 1957, the virus was isolated in tissue cultures from visna infected brain.[6] In an experiment in which four sheep were inoculated by the pulmonary route they showed no signs of spinal fluid changes or histologic lesions in the brain and spinal cord. In three of the four, the virus apparently multiplied somewhere outside the nervous system since neutralizing antibodies appeared in the serum about 3 to 12 months after inoculation. After inoculation, visna virus may be isolated during the preclinical period from both blood and spinal fluid. Visna virus has been isolated from the blood in spite of high concentration of neutralizing antibodies in the serum.

The viruses of visna and of maedi (a chronic pulmonary disease of sheep) appear to be quite similar and have a close antigenic relationship. In tissue culture they produce a characteristic cytopathic effect which leads to complete cell destruction. Visna virus in tissue culture forms syncytia or multinucleated giant cells (Figure 2). The

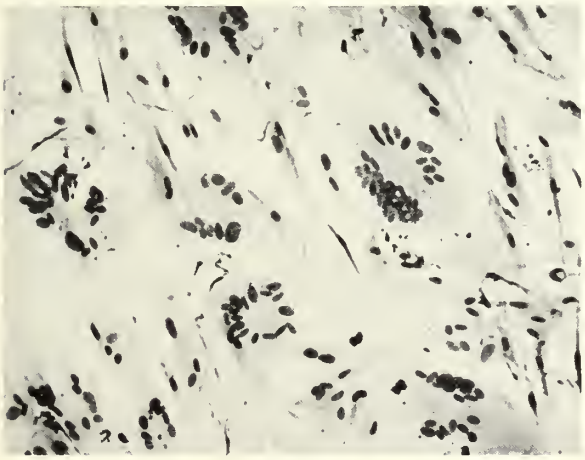

Figure 2.—A photomicrograph of visna virus showing cytopathic effect produced in sheep choroid plexus cells, stained with giemsa. (Picture was provided by Halldor Thormar, and published in Virology 14:463, 1961. Copyright is held by Academic Press.)

demyelination which occurs in visna-infected sheep is similar to certain postinfectious encephalitides in man. Other viruses associated with demyelination such as measles, mumps and canine distemper may also cause giant cell formation in tissue culture. Many of the pathological features —such as lymphocytic and microglial proliferation, perivascular infiltration and demyelination of white matter in addition to the occurrence of multinucleated giant cells—suggest similarities which have been observed in measles encephalitis and in some patients with multiple sclerosis.[7]

Visna antisera with a neutralizing titer of 1:256 failed to neutralize the measles virus, using the sensitive hemagglutination-inhibition (HI) test. Sera from 12 different sheep, considered to be normal and free of disease, likewise failed to reveal measles antibody when tested by the HI method. Indirect fluorescent antibody studies with measles and visna antisera likewise failed to show any relationship. (Unpublished data, J. M. Adams and H. Thormar)

Recently Narayan and associates[8] reported that in American lambs inoculated intracerebrally with visna virus, a persistent infection developed in which the pathologic changes were similar to the early lesions of visna in Icelandic sheep. They concluded that the disease in the experimental lambs might provide a possible model for the study of virus-induced demyelinating disease.

Mink Encephalopathy

On farms in Wisconsin, Washington and Idaho a slowly progressive locomotor incoordination of mink has been known for nearly 20 years. The encephalopathy is characterized by excitability and latent somnolence, rarely with convulsions. The illness is fatal in a few weeks to two months, and the pathologic findings are limited to the central nervous system with evidence of widespread neuronal degeneration, astrogliosis and spongy degeneration of the gray matter.[9]

Following an incubation period of five to ten months, the disease may be transmitted from mink to mink by subcutaneous and intraperitoneal inoculation of either brain or spleen suspensions. The agent is small, unusually resistant to ether and formaldehyde and apparently as resistant to heat as the agent of scrapie. Its similarity to scrapie has suggested that the disease may have spread from infected sheep to mink.

Slow virus infections in animals have not been limited to the central nervous system. For ex-

ample, Aleutian disease of minks is characterized by histiocytosis and bile-duct proliferation. Maedi, which involves the lungs, causes a chronic progressive pneumonia, having characteristics of a slow virus infection similar to visna, both occurring in sheep.

Kuru and Creutzfeldt-Jakob Disease

Studies of Sigurdsson[1] stimulated Gajdusek[10] to pursue the concept of slow virus infection particularly as it is related to a disease known as kuru, which was under investigation. This disease represented an exclusive involvement of the central nervous system in cannibalistic stone-age man in the high interior of New Guinea. Gajdusek[10] estimated that over half of the deaths among the 7,000 South Fore people of New Guinea could be accounted for by kuru.

The clinical features are predominantly cerebellar, including ataxia, disturbed balance and tremor; death occurs in most cases in a few months or less than one year. The patients themselves recognized difficulty in walking and coordination before detection of the disease by physical examination. Shivering was a characteristic symptom. Slurring of speech occurred early and finally resulted in inability to talk. Strabismus and jerky eye movements (but no true nystagmus) were present in children. Mentality appeared to remain normal, but the disease progressed in all patients to death, usually from thirst and starvation, infected ulcers and pneumonia. The pathologic changes in kuru are confined to the nervous system where they are widespread, characterized by a pronounced proliferation and hypertrophy of the astrocytes throughout the brain. Neuronal degeneration is most severe in the cerebellum and demyelination is minimal. Typical astroglosis is shown in Figure 1.

Since the recognition and beginning of investigations of kuru, the high mortality rate has declined significantly. The death rate in children has declined dramatically. Indeed, no child under 12 years of age has died of the disease in the most recent survey, no children are ill with kuru under 14 years of age. This is in striking contrast to the situation when kuru was first recognized; it was then primarily a disease of women and of children of both sexes. The sharply reduced mortality from kuru undoubtedly is related to the great reduction in cannibalism, and suggests virus contaminated brain—this organ considered a particular delicacy by the Fore people.

The clinical features and findings in kuru failed to suggest that the disease might be infectious; however, the successful experimental research with scrapie and visna stimulated Gajdusek and associates to pursue the possibility of a slow virus infection. Hadlow, in 1959, called attention to similarities between scrapie in sheep and the reported symptoms of kuru in man. It was apparent, however, that although transmission studies had been attempted with multiple sclerosis, amyotropic lateral sclerosis, parkinsonism, Schilder's disease and subacute sclerosing panencephalitis, no one had followed their experiments for an extended period of time. In 1966, Gajdusek and associates[11] at the National Institute of Health initiated long-term studies on primates inoculated with suspensions of frozen kuru brain from fatal cases. After incubation periods of 18 to 30 months, seven of eight chimpanzees developed a kuru-like syndrome. Incubation periods in second passage animals ranged from 10 to 18 months.

The duration of the disease did not vary at different passage levels, and remained remarkably similar to the human cases. Gajdusek, Gibbs and Alpers[12] concluded that kuru is a progressive degenerative disease of the central nervous system in man, experimentally transmissible only to the chimpanzee, in which the disease is remarkably similar to that observed in human victims. Kuru, undoubtedly, represents the first clear example of a chronic degenerative disorder of the central nervous system in man that is caused by a slow virus infection.

Gibbs and Gajdusek[13] reported that fatal spongiform encephalopathy occurred in four chimpanzees, 12 to 14 months after inoculation with suspensions of brain from four patients with Creutzfeldt-Jakob disease. Their successful transmission studies strongly indicate that the disease of these patients should be included with the virus infections which may be slow in nature, such as kuru, scrapie and mink encephalopathy. They were successful in passing the disease from chimpanzee to chimpanzee with the same long incubation period. Success was also obtained with an inoculum which had been stored at −70°C (−94°F) for over two years.

All four original patients with Creutzfeldt-Jakob disease died with a similar fatal spongiform encephalopathy, characterized by unremitting and rapidly progressive brain disease with associated severe dementia, disturbances of vision, myoclonic jerks and ataxia. Transmission experiments have

now been successful with brain suspensions from each of six of the eight patients in the original report. The transmissible agent has not been isolated in tissue culture nor has it been clearly identified.

Vernon and associates[14] reported virus-like particles in brain tissue obtained from two patients with Creutzfeldt-Jakob disease. They reported aggregates of nucleoprotein-type filaments which were observed in scattered unidentifiable cytoplasmic fragments or in intracellular spaces.

Further evidence implicating Creutzfeldt-Jakob disease as a slow virus infection was reported recently. A corneal transplant from a 55-year-old man who died with this disease resulted in the death of the recipient from Creutzfeldt-Jakob disease two years later.*

Herpes Group of Viruses

Herpes simplex virus (HSV) type 1 infects most of the population of the United States, usually between six months and five years of age. It is estimated that about 1 percent of those infected suffer mild or severe illnesses lasting one to three weeks. The initial infection is inapparent in the remainder of the population. However, Roizman[15] states that as many as 75 percent of those who have contracted primary infection as evidenced by antiviral antibody are affected at sometime during their lives with recurrent herpetic eruptions. In patients with recurrent herpes infections, circulating antibody almost invariably is present. Lesions tend to occur at the same portion of lips or other areas and persons subject to recurrent herpetic episodes can often predict the recrudescences accurately. It appears clear that following primary infection, the HSV is harbored in an inapparent form at some particular site. Specific stimuli associated with physical or emotional provocations of the host may be manifested in the form of typical herpetic lesions. Perhaps a selective defect in cell mediated immunity is present in these patients.

Of particular interest in these diseases is the mechanism whereby the virus persists in the host in the interval between recurrences. The problem of termination of virus spread is important in view of the apparent ineffectiveness of antiviral antibody. The question arises as to how the infection becomes arrested. It is possible that the virus spreads by direct extension from cell to cell and thus avoids contact with antibody. Interferon and possibly other nonspecific responses of the host may be responsible for termination of the viral infection. It has been ~~been~~ observed by Roizman[15] that cells resistant to HSV produce interferon following infection. Type 2 herpes virus is usually responsible for genital herpes, skin lesions below the waist, neonatal herpes and meningitis.

Cytomegaloviruses (herpes-like) are a major cause of mental retardation according to a recent report by Weller.[16] Indeed he suspects that "we have yet to define the late sequelae of infection with the cytomegaloviruses." Infection by these agents occurs in about 1 percent of newborn infants, but rapidly rises to 10 to 20 percent during the third or fourth month of life; this suggests that infection acquired at birth may become evident slowly. Whether the increasing prevalence with advancing age is a consequence of acquired infection or is related to reactivation of a latent agent is undetermined. Obviously we have much to learn about these common but elusive viruses.

Leider and associates[17] suggested that herpes simplex virus encephalitis is possible, due to a reactivated latent infection. "Since most of the primary herpetic infections which occur in childhood are commonly unrecognized and are not followed by recurrent herpes labialis, it is conceivable that patients without a history of herpes labialis could contract encephalitis from reactivation of a latent infection." Of 52 patients with signs of central nervous system disease in association with herpes simplex virus, they studied 18 subsequently. Of the 18, three had a history of recurrent herpes labialis before the onset of encephalitis, suggesting that their disease may have been a manifestation of reactivation of herpes simplex infection (Figure 3).

A herpes-like virus is associated with Burkitt's lymphoma and may also be linked to infectious mononucleosis (IM), raising the possibility that an extremely common virus may produce malignancy as well as a benign infection, presumably due to differences in host resistance. Recent studies have shown that the Epstein-Barr virus (herpes-like) has growth stimulating capability. Burkitt's lymphoma, a childhood disease occurring in certain areas of Africa, is considered to be the first instance in which an infective agent could be linked to malignancy in man. Peripheral blood lymphocytes from healthy donors, or those with diseases other than infectious mononucleosis, can

San Francisco Chronicle, March 13, and *New York Times*, March 16, 1975.

be cultured only with difficulty, whereas those of IM patients developed readily into permanent lines of lymphoblastoid cells thus suggesting a growth-stimulating effect of the causative agent.

The Epstein-Barr virus (EBV) undoubtedly has worldwide distribution.[18] The Henles found that in about 80 percent of the low-income population in Philadelphia, antibodies to EBV are present. The antibodies appear in some children early in life unassociated with specific illness (presumably the virus producing a silent infection). Further studies soon disclosed a significant association between EBV and infectious mononucleosis (IM). Indirect fluorescent antibody tests also confirmed the association of EBV and IM. Among a group of 150 Yale students, 97 lacked both EBV antibody and a history of IM as freshmen. During the following four to eight years, 28 had frank IM associated with elevated heterophil and EBV antibody responses, and 15 others acquired antibody without evidence of associated illness. Thus the incidence of EBV infection was 44 percent in this population; in contrast none of 53 persons with EBV antibody when they entered Yale subsequently developed clinical IM. Since IM appears to be associated with relatively high socioeconomic standing (being high in college and medical students), the causative agent of IM may be one that spreads early in life, especially under low socioeconomic conditions when the infection might not lead to a characteristic disease but might leave permanent immunity.[19]

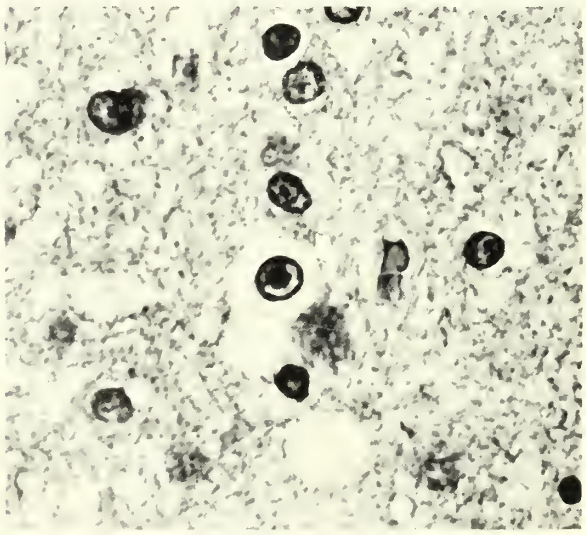

Figure 3.—A photomicrograph showing Cowdry, type A intranuclear inclusion bodies from the right temporal lobe of a patient from whom a strain of type I **herpesvirus hominis** was isolated (reduced from × 855). (Provided by A. Martin Lerner, MD, and taken from an article published by Bailey EJ, Nolan DC, Lerner AM: J of Immunol 104:607-615, 1970. Williams and Wilkins Co., Baltimore, Md. U.S.A.)

Applebaum and associates[20] cite the occurrence of a varicelliform eruption on four of their patients with herpes zoster encephalitis. Von Bokay[21] suggested a close relationship between zoster and chicken pox. The observed occurrence of zoster and chicken pox is considered to represent an unusual clinical response in the same patient to the same virus. By electron micrography, the viral bodies of varicella and zoster are identical in appearance and size.[22] Agents which are indistinguishable from the varicella virus[23] have been isolated from zoster lesions.

Congenital Rubella

Congenital rubella is a chronic, generalized infection, causing frequent defects of the eye (including chorioretinitis, cataracts and glaucoma) and heart (patent ductus arteriosus often with peripheral pulmonary stenosis). Dental abnormalities, microcephaly and mental retardation are also common. The frequency of defects is greatest when infection occurs in the first month of pregnancy. Signs of congenital rubella include primary thrombocytopenia, enlarged liver and evidence of bleeding with petechiae commonly present. The bilirubin may be elevated with fatal termination in some patients.

In utero acquired rubella infection, in contrast to that acquired postnatally, is characterized by a *persistence* of the virus.

In children born with congenital rubella the virus persists despite serum antibodies.[24] Virus may be isolated readily from urine, feces, throat swabs and cerebrospinal fluid as well as from peripheral blood, bone marrow, lens tissue and middle ear fluid. Viral persistence tends to terminate spontaneously when the child reaches about 12 to 18 months of age. Virus has been isolated postmortem from essentially every organ and gland examined including the brain, and tissues obtained postmortem and grown in tissue culture were found to be infected with rubella virus. The virus was not cytolytic; both the cells and virus survived for many months establishing virus carrier cultures.

Although the virus-infected cells were morphologically indistinguishable from noninfected cells, examination of the infected cells indicated that they had a slower growth rate. Doubling time of infected cells was 48 to 72 hours as compared

with 24 hours in noninfected cells. The noninfected cells could be maintained for about 40 passages while infected cells could only be maintained for 20 passages. Thus, not only was growth rate of the infected cells affected by the virus but the ultimate doubling potential of the cells was also reduced. Careful analysis of the virus-carrier cultures showed that every cell in the culture was infected. Rubella antiserum added to the culture fluid did not rid the culture of virus. These findings suggest that the virus was passed from parent cell to daughter cell during cell division.

Organs of infants with congenital rubella contained fewer cells than organs from infants without congenital rubella. The cells appear normal in size and shape but were present in subnormal numbers. Involvement in early embryonic life would result in a slower growth rate and thus smaller organs and a smaller baby. A significant correlation was found between failure to thrive and virus persistence.

Cells derived from embryonic tissues are neither sensitive to nor capable of producing interferon. The possibility exists that in early embryonic life the cells of the human fetus are not capable of an interferon response upon exposure to the rubella virus. The chronically infected cells appear to be refractory to interferon systems since they could not be stimulated to produce interferon when superinfected with another virus which readily produced interferon in noninfected cells. A parallel exists between the persistent infection in rubella and that which has been established with lymphocytic choriomeningitis infection in mice. It appears that chronicity may occur only by acquiring the virus *in utero* or neonatally.

The neurological aspects of congenital rubella were studied in 100 infants by Desmond and associates,[25] who found evidence of central nervous system involvement in 81 of 100 infants studied. The infants were lethargic and irritable with tone disturbances, seizures and delays in motor development and socialization. A full fontanel, increase in concentration of spinal fluid protein and persistence of the rubella virus in spinal fluid were the outstanding manifestations of encephalitis. Twenty of the patients died, but 64 were followed regularly for 18 months, at which time 69 percent had some degree of neurological impairment. At postmortem, the most prominent lesions were leptomeningitis, vasculitis and multiple focal areas of necrosis and perivascular calcification (Figure 4).

Possible Slow Virus Infections of Man

Amyotrophic lateral sclerosis (ALS) has been described as a syndrome with symptoms and signs of lower and upper motor neuron degeneration rather than a single disease entity. Kurland[26] outlined three groups or types of ALS: (1) classic or sporadic, (2) familial and presumably hereditary and (3) Mariana Islands form. He observed that in the hereditary form there is predilection for males not present in the other types. Also in this form there is a greater likelihood that the initial weakness and wasting will occur in the lower extremities. Demyelination of the posterior columns is signifiant without sensory changes; the histochemical changes in the skin described in some forms have not been observed in the familial or hereditary type, in which a family history may show a pattern compatible with dominant inheritance. In the Mariana Islands the disease tends to occur more often in younger persons than in the classical form, and spasticity is more likely to be present initially.

The first concept of ALS on the island of Guam was that the disease was genetic in origin, but the recognition of ALS in other Western Pacific Islands suggested a possible exogenous factor. Further epidemiologic studies in the Pacific Islands as well as elsewhere are clearly needed.

Viral Hepatitis

The viral cause of infectious hepatitis remains to be proved, but the possibility that serum hepa-

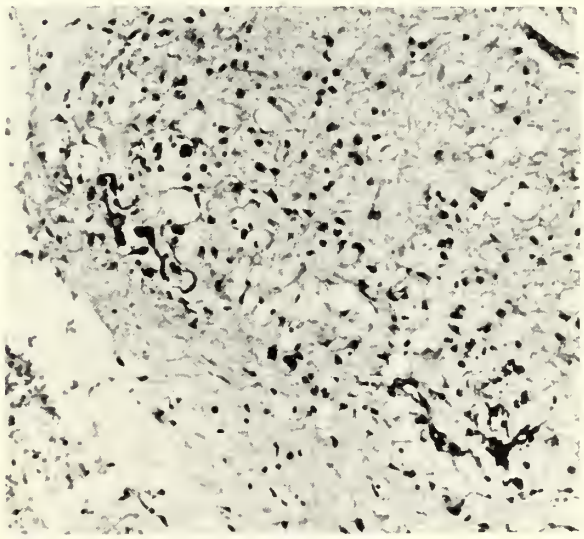

Figure 4.—A photomicrograph from a patient with congenital rubella showing a focal area of necrosis and perivascular calcification. (Stain: hematoxylin-eosin, reduced from × 580.)

titis (SH) is a slow or latent virus infection seems to be widely accepted. Serum hepatitis differs from infectious hepatitis (IH) in many clinical epidemiologic and immunologic respects. The incubation period of SH ranges from about 50 to 180 days; it may occur in any season, infecting all age groups.[27]

The recent discovery of Australian antigen, also referred to as hepatitis associated antigen (HAA) or hepatitis B antigen (HB) is a major advance in this still very confused group of diseases. The immunodiffusion and complement fixation tests for HAA are useful in some cases in differentiating SH from IH and in identifying the carrier state following SH infection. The hepatitis agent is highly infectious; the tests available for HB have practical value in detecting the antigen in blood banks and in screening potential donors.

" . . . though the discovery of Australia antigen and the establishment of its link with SH represents a major breakthrough in hepatitis, we remain several breakthroughs removed from a more complete understanding of the etiology of either IH or SH."[27] The hepatitis viruses are now designated type A for infectious hepatitis and type B for serum hepatitis. The type A virus has been transmitted to marmosets and type B to chimpanzees. A specific hepatitis B immune serum globulin is now under trial for passive immunization and standard gammaglobulin is used to prevent type A hepatitis. It is interesting to note that at a recent symposium on viral hepatitis held in Milan, Doctor Maurice R. Hilleman, of the Merck Institute for Therapeutic Research, showed for the first time electron microscopic pictures of the hepatitis A virus which is smaller than the B type.

Vaccinia Virus in Central Nervous System Disease

One recent study[28] showed vaccinia virus neutralizing antibodies in the cerebral spinal fluid (CSF) of 30 percent of 187 patients with multiple sclerosis; in only 3 percent of 87 patients with other neurologic diseases, and in none of 30 normal control subjects.

A case of neuromyelitis optica (Devic's disease) was reported by Adams and associates[29] in which the vaccinia virus was directly implicated 11 years after primary vaccination of the patient against smallpox. Antibody titers against vaccinia virus were extremely high in the patient's serum (1:5,000) on several occasions before death; likewise, very elevated titers were found in CSF, ranging from 1:16 to 1:64. Brain tissue, obtained promptly following death, was inoculated along with Freund's complete adjuvant subcutaneously into three rabbits. In all three, vaccinia antibodies developed, whereas in ten control animals there was no antibody response. Subsequently, three rabbits were inoculated in a similar fashion with normal brain tissue plus adjuvant and viral antibodies failed to develop. To our knowledge, this patient represents the first known case in which the vaccinia virus may play an etiologic role in severe demyelinating disease.

At postmortem, the brain showed a severe form of subacute disseminated sclerosis and the presence of Guarnieri's bodies, typical of infection caused by vaccinia virus. Much further study of patients with demyelinating disease will be required before the role of vaccinia virus and other possible persistent agents such as the measles virus can be implicated as etiologic agents in degenerative brain diseases.

The pathological findings in variola and vaccinia encephalitis appear to be identical.[30] The commonest neurological syndrome in these conditions is that of disseminated encephalomyelitis. In 1968, it was pointed out by Osuntokun[31] that "neurological complications of smallpox vaccination are more likely to occur in infants (under 1), after primary vaccination and in adults revaccinated after a long interval following primary vaccination in childhood."

Persistence of Measles Virus and Demyelinating Disease

The primary demyelinating disorders have posed a singularly intractable problem for the physician; their classification is unclear and their cause, until quite recently, was unknown. It now appears that many and perhaps all of these disorders—that is, multiple sclerosis (MS), subacute sclerosing panencephalitis (SSPE) and neuromyelitis optica (NO)—may not be primary at all, but represent long-delayed sequelae of viral infections.

Viral infections in general, and measles rubeola in particular, may severely affect the central nervous system (CNS). Meigs and Pepper in 1877[32] described a number of atypical measles cases with such encephalitic symptoms as violent nausea and vomiting, frontal headache, delirium and convulsions. Measles encephalitis appears within a few days of the infection and ends, in one way or an-

other, within days or weeks. The condition can persist and progress for months or even years. That some protracted cases of encephalitis are caused by persistent infection with measles virus, rather than by some other concomitant agent or process, has been shown by portmortem studies in which CNS tissues show characteristic traces of the virus: multinucleated giant cells and inclusion bodies in both the cytoplasm and nucleus (Figure 5). The same cytological changes have been observed in other viral diseases—for example, canine distemper and rinderpest (a disease of cattle), both have symptomatologic and immunologic similarities to measles. A disease of mature dogs known as old dog encephalitis (ODE) has been shown to be similar immunologically and pathologically to distemper and measles and consequently is of importance as a possible animal model for the study of severe demyelinating diseases of human beings such as MS, SSPE and NO.[33]

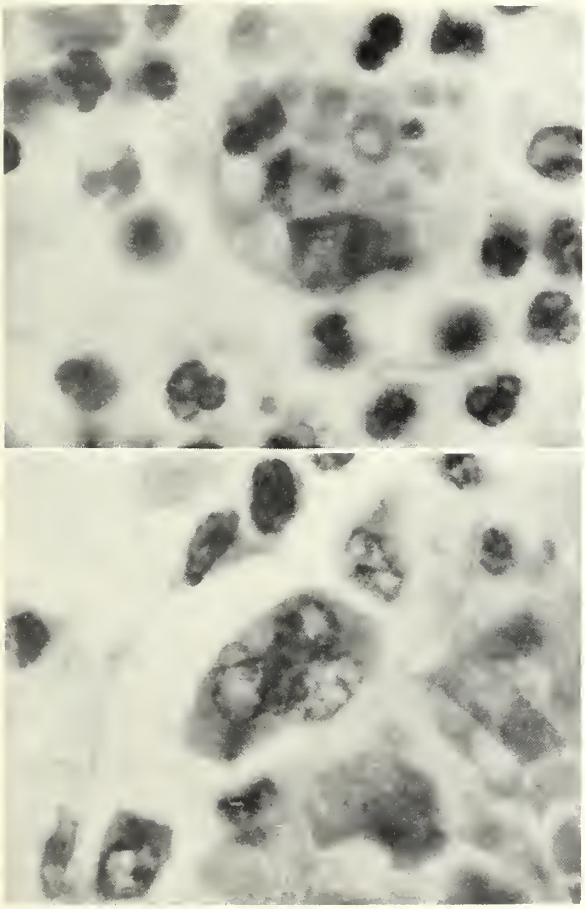

Figure 5.—Upper, Photomicrograph from the meninges of a child, age 13 months, who died following measles encephalitis, showing a multinucleated giant cell with cytoplasmic and intranuclear inclusion bodies. (Stain: hematoxylin-eosin, reduced from × 2100.) **Lower,** Photomicrograph from a 5½-year-old child who died following measles encephalitis, showing a small multinucleated giant cell in the perivascular space. (Stain: picro-Mallory reduced from × 2100.)

Two other features of measles encephalitis merit mention. First, in all but the most fulminating cases, where death intervenes very rapidly, a consistent pathologic feature is demyelination, often accompanied by scarring; this feature is probably responsible for the high incidence (up to 50 percent) of permanent neurologic impairment in patients who survive the initial encephalitis. Second, it appears that the affinity of measles virus for the CNS may be far greater than the infrequency of frank encephalitis (0.5 percent or less of all measles cases) would suggest. Electroencephalographic studies of patients with measles indicate that in from 30 to 50 percent there are temporary brain-wave changes characteristic of those seen in unambiguous encephalitis cases.[34]

Measles encephalitis can in many cases be classed as a demyelinating disease and, in at least some cases, as subacute or chronic progressive disease—as can vaccinia encephalitis and the other encephalitides associated with childhood diseases. It is possible that some or all of the other chronic demyelinating diseases might result from the same or related processes. This concept is strengthened by the pronounced similarity between some forms of primary demyelinating disease and certain conditions clearly linked to viral infection. For example, Ferraro[35] found no significant difference, clinical or pathologic, between acute multiple sclerosis and subacute varieties of postexanthematous and postvaccinal encephalomyelitis. Similar observations have been made by other investigators.

The fundamental observations of J. M. Charcot established neurology on the basis of pathological changes.[36] His students (Pierre Marie probably being the most eminent) continued to expound his teachings and correlated typical symptom complexes with neuropathological findings. In 1895, Pierre Marie,[37] in lectures to the New Sydenham Society, London, stated: "Eruptive fevers must also be mentioned, namely measles, scarlatina, and above all—smallpox. Cases are numerous in which insular sclerosis has been known to occur during convalescence after the affection: tremor in the limbs with more or less paresis, disorder of speech which becomes slow and scanning, nystagmus and in short, all the characteristic symptoms

of insular sclerosis may exist. At times these symptoms cease and entirely disappear, but they may also continue and confirmed insular sclerosis occurs."

In 1912 Schilder[38] reported a very slowly progressive degeneration of the white matter characterized by demyelination in the main parts of the brain. Similar cerebral sclerosis has since been reported by Scholz,[39] Balo[40] and Greenfield.[41] It is apparent that neuromyelitis optica and disseminated sclerosis exhibit certain similarities to these conditions. The reason for grouping them together is that the histologic changes are, in their incipiency, of the same nature in all.

A common feature of many of these diseases of the nervous system is the presence of foci of destruction of the myelin sheaths of the nerve fibers. The areas of destruction vary in size, shape and distribution, and also in the acuteness of the pathologcal process. Lord Brain[42] points out that "the axis cylinders often suffer as well as their myelin sheaths . . . the most acute forms often follow acute infections, especially the exanthemata caused by viruses such as measles, smallpox, and vaccinia."

Measles encephalitis (ME) was studied in its acute, subacute and chronic forms and evidence of invasion by the measles virus was indicated by the hallmark of the virus, namely, intranuclear and cytoplasmic inclusion bodies and multinucleated giant cells (Figure 5). The studies provided evidence for persistence of the measles virus months and years following the initial measles illness. These findings were reported by the writer early in 1966.[43] Following this report, several studies on Dawson's "inclusion encephalitis" appeared in 1967 pointing directly to an etiologic association with measles virus. Connolly and coworkers[44] reported high levels of measles antibody with rising levels as the disease progressed. They were also successful in demonstrating specific fluorescence of inclusion bodies in nerve cells by measles antibody, indicating clearly the presence of measles virus in some form.

Dawson[45] reported two cases of "inclusion encephalitis" characterized by involuntary jerking movements of the limbs and mental regression and by the presence in many brain cells of intranuclear inclusion bodies. Examination showed a diffuse inflammatory reaction in the white matter in certain areas of the brain. The characteristics of the inflammation are those of viral encephalitis. The areas of damage to the white matter may resemble to some extent the early stages of Schilder's disease. Perivascular infiltration with lymphocytes and plasma cells occur both in the gray and the white matter. Both nuclear and cytoplastic inclusion bodies may be found in the same cell, or one type may occur without the other.

These patients have very high levels of measles antibodies in their serum and spinal fluid, indicating the overwhelmng nature of their infection. In recent brain biopsy studies, inclusion bodies similar to those found in measles encephalitis are present and are found to be positive for the presence of measles virus when examined by the fluorescent antibody technique. Electron microscopic studies of brain sections have shown filaments or tubules similar to the structure known to be present in measles infected cells.[46,47]

An early clue to the origin of subacute sclerosing panencephalitis came from the inclusion bodies that gave it its original name. These are seen in both the nucleus and the cytoplasm—a phenomenon now known to be uniquely associated in man with measles virus. In the late 1960's, several investigators began following up the possible relationship of measles and SSPE. They demonstrated high levels of measles antibodies in both the serum and especially the spinal fluid of patients with SSPE. More important, they turned up conclusive evidence of measles virus in the brain tissue of some terminal cases.[48-50]

The presence of measles virus has been shown by a variety of techniques. The inclusion bodies are positive for the virus when tested by the fluorescent antibody technique. Electron microscope studies of brain sections have shown filaments or tubules similar to the structures known to be present in measles infected cells[46] (Figure 6). The measles virus has been identified by propagation of the patients' brain cells and co-cultivation with other cell lines such as HeLa, human embryo kidney and green-monkey kidney cells. Many details of the pathologic processes in SSPE are still obscure, but that measles virus *in some form* is deeply implicated seems beyond question. Presumably, this disease may represent a genetically determined defect in cellular immunity to the measles virus.

Multiple sclerosis strikes most commonly in the years between 20 and 40, although it is known to occur occasionally in children. It appears to be influenced by latitude in both hemispheres and is more common in the temperate zones than the tropics. It also seems to be associated with par-

ticular localities rather than with any special group of persons living there. The epidemiology of measles encephalitis is unknown, but the meager information which is available would correspond to what is known about MS. Graphs constructed by epidemiologists have suggested a relationship of MS to a common childhood illness probably caused by viruses. Their studies show that the latent period of the disease is prolonged and may extend over decades.

Dean states that "an environmental factor would appear to be mainly responsible for multiple sclerosis, and this environmental influence may be associated to some extent with latitude."[51]

Other epidemiologic studies have focused on the familial occurrence of MS and have determined that the incidence of the disease in families where a parent or a sibling already has the disease is something like eight times normal (general population) incidence.[52]

However, these data are consistent with what one would expect of some environmental agent exerting its influence in childhood—specifically, a virus that could be transmitted from child to child, less often from parent to child, and never, or almost never, from parent to parent. Operating on this assumption, Poskanzer[52] has calculated from a summary of known cases in siblings that the disease, if acquired from a common exposure in childhood, would have an incubation period averaging about 21 years (with the range of incubation from 12 to 32 years).

Can measles virus remain latent in the human body for as long as 21 years before causing clinical manifestations? There is evidence that it can. In some cases of SSPE, the disease developed many years after childhood measles. Enders-Ruckle[52] reported that persistent virus has actually been isolated from lymphoid tissues (lymph nodes and spleen) in a monkey and two adult humans—all three possessing naturally acquired measles antibodies. A genetic defect resulting in a selective defect in cellular immunity to the measles and related viruses is postulated. The defect may represent immunodeficiency of the T cells making it difficult for the patient to eradicate the infectious agent. The defect may be associated with the presence of the LD-7a determinant. In collaboration

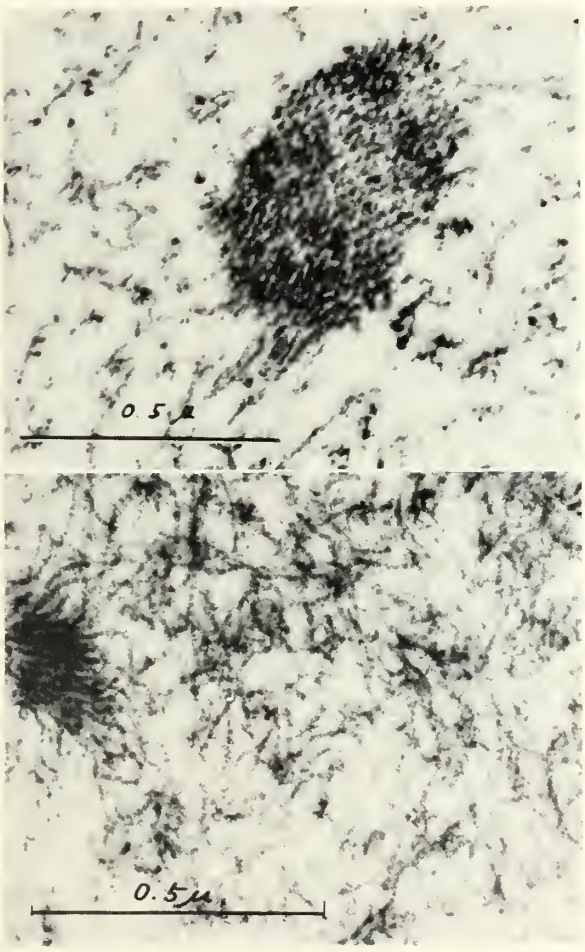

Figure 6.—Electronmicrographs of the fine structure of the measles virus (made from specimens of infected tissue cells) show filaments of high density which are frequently seen in a crystalline arrangement (reduced from × 126,000). (Republished by permission from Adams JM: Persistence of measles virus and demyelinating disease. Hosp Pract, May 1970)

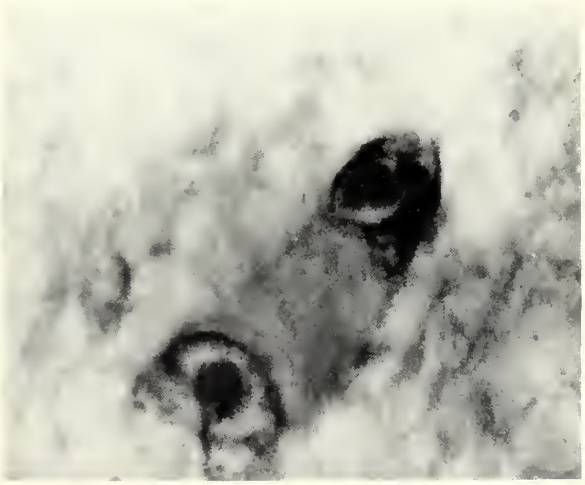

Figure 7.—A photomicrograph from a 14-year-old child who died from sequelae of measles encephalitis which occurred at the age of 6 years, showing an astrocyte with two intranuclear inclusion bodies. (Stain: hematoxylin-eosin, reduced from × 2100.)

with Finkelstein and Walford we found that the histocompatibility antigen type HLA-7 was overrepresented in 64 patients with MS. This finding is compatible with the results reported by others.[54]

Previously we described two children with fatal measles encephalitis in whom were seen the hallmarks of measles: characteristic inclusion bodies and multinucleated giant cells 8 and 11 years after their initial encephalitis[55] (Figure 7).

In 1966, Rustigian[56] reported that measles virus persisted in HeLa cell cultures for up to 500 generations, over a period of six years. Continued subculturing led to a virtual disappearance of the virus's destructive effect, as well as to a decrease in the amount of virus recovered from the persistently infected cells. The virus could persist for long periods when in the presence of high levels of measles antibody. In this case, the infected cell developed a "non-yielder" state, in which there was no detectable virus that could infect normal cultures. Yet virus continued to be synthesized intracellularly and to form characteristic inclusion bodies. Rustigian[56] described this anomalous virus as incomplete, lacking all or part of its normal protein envelope; virion apparently was passed from cell to cell in the course of normal cell division.

It is apparent that the epidemiology of MS shows certain suspicious features—some of them similar to those of measles encephalitis. It is likewise clear that some viruses, in particular measles virus, can persist in cells over long periods, both *in vitro* and *in vivo*. Finally there is evidence that in some persons the measles virus cannot only persist but can cause demyelinating disease (such as SSPE) after a relatively lengthy asymptomatic period.

The hallmark of the measles virus has shown up on postmortem brain sections from some patients with MS.[57] As mentioned earlier, inclusion bodies and multinucleated cells have also been found in measles encephalitis as well as in SSPE and in animals infected with the related distemper and rinderpest viruses, measles virus and the like. Measles virus may be one cause but not the only cause of MS. The disease could be produced by similar persistent infections with other agents or combination of agents. This disease may occur only in persons with a genetically determined defect in cellular immunity to measles or related viruses. However, we must know much more about the possible relationship between the virus and the CNS pathology in MS, before reaching definite conclusions. Demyelination might result directly from viral damage to the cells, but it might instead be due to an antigen-antiviral antibody complex postulated in some other demyelinating diseases.

The importance of optic neuritis (ON) has been emphasized recently by McAlpine,[58] Link and associates[59] and Arnason.[60] This event is not uncommon in childhood, particularly in association with childhood diseases such as measles, and acute respiratory diseases of viral origin. When patients are followed for many years, the early signs of multiple sclerosis (MS)—often vague and confusing—should be seriously considered. The long-range follow-up of ON has eventually led to a diagnosis of MS. The occurrence of optic neuritis at some time during the course of disease in every patient with MS is not unusual and when it occurs early in life, recovery may be complete.

Summary

Outstanding contributions in the field of veterinary medicine led to the discovery of transmissible agents as the cause of a new group of human diseases. Persistent virus infections of sheep such as scrapie and visna, and mink encephalopathy, stimulated a search for the infectious cause of human neuropathies. Kuru, a disease of cannibalistic tribes in the highlands of New Guinea, and Creutzfeldt-Jakob diseases are now clearly shown to be infectious in nature with long incubation periods. The pathologic changes in each are apparently limited to the nervous system.

Other slow, latent and temperate infectious diseases are possible candidates for inclusion in the category of persisting viral infections. Evidence for persisting infection in congenital rubella and cytomegalovirus infections in the newborn is established in spite of high antibody titers. The herpes group of viruses (which includes cytomegalovirus) is recognized as causing possible recurrent, latent and temperate infections. Many of the same characteristics are evident in infectious hepatitis type A, and serum hepatitis type B.

The possibility that measles may become a slow or persistent infection is supported by immunological and pathological findings in experimental studies as well as in man. Several clinics have reported increased levels of measles antibodies in the sera and spinal fluid of many patients with subacute sclerosing panencephalitis and multiple sclerosis. Measles virus has been isolated from patients with subacute sclerosing

panencephalitis, occurring years following childhood measles. Clinical concepts in the early literature support the relationship of measles and primary demyelinating diseases.

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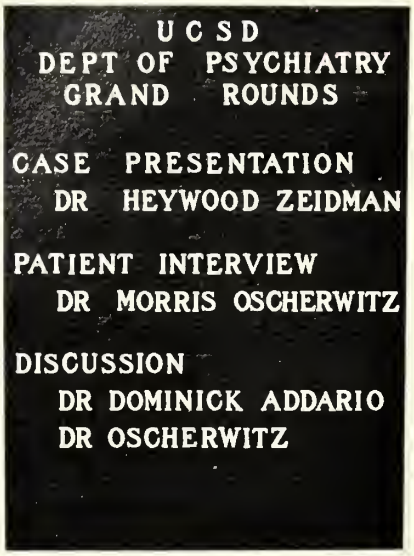

Amphetamine Psychosis or Paranoid Schizophrenia?

Based on Psychiatric Grand Rounds held at University Hospital, San Diego, a teaching facility of the School of Medicine, University of California, San Diego, in November 1973; edited by Barbara Blomgren, BA, and Leighton Huey, MD.

DR. ZEIDMAN:* Harold Leonardo† is a single 44-year-old airplane mechanic who was admitted to the hospital for his first psychiatric treatment nearly 12 weeks ago. He was brought to the emergency room by his aunt and uncle after his release from jail, where he had been booked on a charge of assault with a deadly weapon.

Hal has had diabetes since 1970. His general practitioner prescribed chlorpropamide (Diabinase®) for control of glucose, and anorexics and diuretics for control of weight. In January of 1971 Hal started taking mild anorexics such as diethylpropion hydrochloride (Tepanil®), but by October of that year he began using amphetamines. He has been taking dextroamphetamine and methamphetamine steadily since that time, usually in combination with barbiturates. The prescribed amounts were about 15 mg of amphetamine per day; how much he actually used is hard to say. During that period his weight fluctuated widely. After some time on these compounds Hal began to have strange experiences.

He describes an incident when he returned to work one evening to pick up a tool. He noticed men going up a staircase that led to the area reserved for stewardesses. As he was leaving the work area he saw two black cars filled with men following him. One of the cars had an airline decal on it, and he believes it followed him because of something he might have seen while getting his tool. He thinks that maybe the stewardesses were involved in a prostitution ring. These cars continued to follow him until he came to San Diego from his home in Los Angeles. About the same time he began calling the young daughter of his foreman a whore. Until then he had been friendly with his foreman and lived in an apartment behind his house. Hal frequently had dinner with his foreman's family. After the name-calling incidents he was placed on medical leave from the airline and told to seek psychiatric help.

Soon thereafter he heard voices telling him that his aunt and uncle in San Diego were in danger. He drove here and stayed with them two weeks without incident. One evening he could not sleep and stayed up all night talking to his aunt and preparing to return home. That night he noticed

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†The patient's name is fictitious.

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creeping things on the curtains and coming through the screens. He also felt that the plants could marry people.

While driving toward Los Angeles the next day he heard the trees telling him that his aunt and uncle were in danger; the bigger the tree, the louder the voice. He headed back to his relatives' home. He thought that the plants were holding the family hostage. When he arrived he walked around the house and peered through the windows. He took his unloaded gun from the car, and at that point a neighbor came by to see what was happening. He leveled the gun at her, not sure whether she was allied with the plants or not. She in turn ran into her house and called the police, who arrested Hal.

Hal has never been married. Both parents, in their seventies, have diabetes. He believes he had a good relationship with them, although his father was very domineering. He lived with his parents in New York until five years ago, when he had difficulty getting along with a younger brother who also lived at home. At that time Hal moved to Los Angeles. His parents later moved to San Diego for two years; just before the recent events began they returned to New York with the younger brother, who could not find work here.

Hal is the oldest of five children, and although he is in contact with his siblings he does not describe a close relationship with any of them. There is no evidence of psychiatric disease within the family, although the younger brother does seem to have a violent temper. The patient started school late because of an asthmatic condition. Because of his asthma he lived on Long Island, with the aunt who is now in San Diego, from his fifth to his seventh year. He left school in the tenth grade to join the Air Force. After leaving the service, he completed high school and attended school to become an airplane mechanic. He has been employed with the same major airline for 18 years.

Hal thinks of himself as a loner. He describes one close relationship with a girl when he was 17 years old. He thought he loved her and planned to marry her, but she died suddenly of pneumonia. Around that time, his aunt intercepted a letter he wrote to his mother suggesting that they have sexual relations. (The letter was never forwarded to his mother, and Hal is unaware that anyone else knows about it.) At present his only sexual contact is with prostitutes. He collects pornographic material, and while he was recuperating on the ward he began to post *Playmate* pictures around his room.

Hal denies abusing any drugs, but he explains that the mechanics often drink the liquor found aboard the planes. They keep an unofficial tally as to who drinks how much. He states that when he became the number two man on the shop list of drinkers he decided it was time to stop.

While on the ward he was placed on trifluoperazine hydrochloride (Stelazine®) and did well on 5 mg twice a day, although he remained superficial and aloof. After two weeks he insisted on leaving the hospital. Close follow-up was arranged, and he kept his first appointment as scheduled two days after discharge. We later discovered that he thought that the medications were poison and stopped taking them. There was also a hint that he had been drinking, but no determination of alcohol level was made at that time, nor had one been made on his first admission.

On the fourth day after discharge he was returning to Los Angeles when he felt a strong urge to go to church. There, over the altar, the patient saw himself nailed to the crucifix and apparently rising to heaven. The vision alarmed him, and he returned to his aunt's home, but, instead of visiting her, he approached the neighbor's house and attempted to break in. He was returned to the ward, where he remained paranoid, delusional and hallucinating despite administration of increasing amounts of phenothiazines for two weeks. He then cleared and seemed ready for discharge, but he suffered a relapse of hallucinations and delusions while awaiting placement after one month of continued medication and apparent improvement. He now appears to have no active hallucinations or fresh delusions, but it was thought best to place him in a board-and-care facility, which is where he came from today.

At admission, the emergency room resident felt the patient was probably suffering from amphetamine psychosis. During staff rounds the attending psychiatrist felt he was experiencing a true schizophrenic attack. Later a court-appointed psychiatrist felt he had a toxic psychosis. Results of a Minnesota Multiphasic Personality Inventory (MMPI) were interpreted as showing "schizophrenic reaction or schizophreniform psychosis." It was also noted that he had a strong potential for drug or alcohol abuse. He now is receiving fluphenazine hydrochloride (Prolixin®) given intramuscularly, and the difference in his mental status is striking. He is not as buoyant as he was when

he first came into the hospital, but he continues to believe in the delusion of being followed in Los Angeles.

DR. WEINBERG:* I can add some observations about the patient's behavior during his second stay in hospital. That first month was pretty hectic. On oral medication his mental status fluctuated almost daily. One day he would be hostile, belligerent, sarcastic, difficult to get along with and very threatening. The next day he would be mild-mannered and meek, a model patient. He demanded to leave the hospital on a number of occasions; the only way we could keep him there was by pointing out that with his legal problems he was safer in the hospital than he would be in jail. After about a month we started him on intramuscularly administered Prolixin because we thought that he probably would stop taking oral medication as he had after the first stay in hospital. We stabilized him on one weekly injection of 25 mg, and he did pretty well until about three weeks before discharge.

One day he said he was afraid he was going to be sent to the state hospital and if that happened, he was going to go to New York to take out a contract on my life—because he felt I would be responsible. The next day he came in and said he did not know why he ever said that; it was a very frightening thing for him. It was also very frightening for me! That was the last really hostile outburst we heard from him until we got ready for discharge. At that time he became resistant and was constantly thinking why he should not go one or another place, and changing plans about where he should go, and when, and about who should follow him. He asked to make out a second MMPI, which he did, and Dr. Storms† thought it showed that he was hallucinating and very depressed and anxious, but not as paranoid or delusional as earlier. I confronted Hal with some of the material on the MMPI and he said that he was not able to tell me exactly, but he felt that the voices were coming back. He was feeling very frightened again; in fact he cried, something I had never seen him do before, and he sounded depressed and anxious and did not want to leave the ward. We put off discharge for about a week, and increased the Proxilin dose a little bit, and he seemed to do well. By the time of discharge he was willing to leave the hospital. I think it's interesting how well he had adapted to the hospital; he was very attached to many of the staff. It was hard for him to get used to the idea of leaving a place that had become familiar for him.

DR. ZEIDMAN: That part about his being afraid of going to the state hospital was not unrealistic; the court wanted to send him to a state hospital. The law of California states that if a person is judged not guilty of a crime by reason of insanity the State is required to send him to a state hospital for 90 days if he still is psychotic at the time of judgment, no matter where else he is receiving treatment.

(The patient was escorted into the room and introduced to Dr. Oscherwitz, who interviewed him before the residents and staff.)

DR. OSCHERWITZ:* Hi, Mr. Leonardo.
Patient: Hi.

DR. OSCHERWITZ: I'm Dr. Oscherwitz. We're going to do a little talking. Would you mind putting this [microphone] on?
Patient: I'm a little afraid of it.

DR. OSCHERWITZ: Are you? Why don't you have this seat? We're doing a tape recording of our teaching session here. Is that all right?
Patient: Okay.

DR. OSCHERWITZ: Dr. Zeidman has told us something about your hospitalization and some of the problems you've been having. How are you feeling now?
Patient: I'm feeling great, ready to go to work.

DR. OSCHERWITZ: Ready to go to work—back to the airline?
Patient: Yep.

DR. OSCHERWITZ: Where would that be, in Los Angeles?
Patient (promptly): Los Angeles.

DR. OSCHERWITZ: Things are pretty well back in place?
Patient: I think they're pretty well settled, yeah.

DR. OSCHERWITZ: Can you give me some idea of what happened, what your understanding is of the event?
Patient: I don't know what happened. It just piled up all of a sudden like. I musta went haywire or something. I heard trees and everything talking to me as though they weren't really normal.

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DR. OSCHERWITZ: That must have been very frightening.

Patient: Yes, it was. I turned around twice to come back, and I don't know what happened. Then I took a shotgun and I went in this friend's and was picked up by the police.

DR. OSCHERWITZ: What were you doing at that time with the shotgun? What was your idea?

Patient: Well, I came back because the voices told me that my aunt and uncle and my niece were being held as hostages, so I came back and I had a shotgun in the back of my car and I pulled that out.

DR. OSCHERWITZ: To protect your aunt and uncle and niece?

Patient: Right. And I asked the woman next door for help. Instead she turned me in as assault with a deadly weapon.

DR. OSCHERWITZ: Who were you protecting your aunt and uncle and niece from?

Patient: Plants and trees.

DR. OSCHERWITZ: How do you understand that now?

Patient: I don't know. I don't believe it any more. I just put it out of my mind. It couldn't be possible.

DR. OSCHERWITZ: I see. Now I understand that this started around the time that your parents went back to New York. Is that true? Did the difficulties begin around that time?

Patient: Around that time, yes.

DR. OSCHERWITZ: Can you explain to me the relationship that you have with your parents and that your younger brother has? My understanding is that . . .

Patient (interrupting): Well, my younger brother changes with the full moon.

DR. OSCHERWITZ: Yeah?

Patient: He can be radical, or, you know, rational.

DR. OSCHERWITZ: How old is he?

Patient: About 30.

DR. OSCHERWITZ: He's the youngest and you're the oldest?

Patient: I'm the oldest.

DR. OSCHERWITZ: Now, you were with your folks in New York City up until you were 39, is that right?

Patient: 38.

DR. OSCHERWITZ: 38. And you left because of some disagreements with him?

Patient: Yes. I couldn't get along with him so I moved out of the house.

DR. OSCHERWITZ: You moved out, and he stayed with your folks. Just him, the other . . .

Patient: Just him. The others were already out.

DR. OSCHERWITZ: The other three were already out. And then what happened? Did you come out here?

Patient: I came out here to live. And everything was stable for about two years, and then they moved out.

DR. OSCHERWITZ: Your folks moved out.

Patient: Yeah, and then it got unstable again.

DR. OSCHERWITZ: Why did they move out?

Patient: Uh, I don't know. They just sold their house after so many years, and they wanted to make a move.

DR. OSCHERWITZ: And then things got unstable out here then. Did your brother come with them?

Patient: Oh, yeah. He became the dominating force. He didn't go to work any more. Whenever he wanted to throw you out of the house he threw you out. In other words, they put him in charge.

DR. OSCHERWITZ: They let him take over?

Patient: Yeah, their lives.

DR. OSCHERWITZ: And that affected you because . . .

Patient: Well, that affected me because I didn't like that. I wanted my father to be free.

DR. OSCHERWITZ: I see. Your brother dominated him.

Patient: Yeah. Him and my mother too.

DR. OSCHERWITZ: And then they went back to New York City?

Patient: They went back in February of this year.

DR. OSCHERWITZ: Why did they go?

Patient: Well, they thought the doctors were better on the East Coast.

DR. OSCHERWITZ: For whom?

Patient: For themselves.

DR. OSCHERWITZ: Are they sick?

Patient: I guess they are. Both of them have heart trouble.

DR. OSCHERWITZ: Both of them have bad hearts . . . and so they're back there now with your brother.

Patient: Yeah, and now they wanta come back out here.

DR. OSCHERWITZ: Now they wanta come back. What do you think about that?

Patient: Well, that's up to them. I can't control that.

DR. OSCHERWITZ: With or without your brother?

Patient: I don't know. I might imagine he'd come with them.

DR. OSCHERWITZ: So, in other words, things were tough in your life when they came out here, and they got even tougher when they went back?

Patient: When they went back.

DR. OSCHERWITZ: Was it during the years that they were out here that you started taking the drugs?

Patient: No, no. I had taken the reducing tablets about two and a half years ago.

DR. OSCHERWITZ: Um hum.

Patient: Maybe it was *about the same time they decided to come out.*

DR. OSCHERWITZ: Did those medicines help you feel better around them and around your brother?

Patient: Well, they made me reduce a lot. That's about all.

DR. OSCHERWITZ: Didn't do anything to help your feelings?

Patient: No, I don't think so.

DR. OSCHERWITZ: Did you get pretty angry with your brother at times?

Patient: Oh, yeah.

DR. OSCHERWITZ: But how bad would it get?

Patient: Bad enough to throw a hatchet at you.

DR. OSCHERWITZ: Who did the throwing?

Patient: He did.

DR. OSCHERWITZ: He threw a hatchet at you?

Patient: Yeah, and missed me about an inch.

DR. OSCHERWITZ: When was that?

Patient: Oh, about maybe a year and a half ago.

DR. OSCHERWITZ: Was he this violent with your parents?

Patient: I don't know. I wasn't there.

DR. OSCHERWITZ: Okay. I just want to clear that up. I thought that was very important in terms of these problems. Do you think it probably is?

Patient: It might have.

DR. OSCHERWITZ: So, in other words, when you became upset it was around the idea of protecting your aunt and uncle?

Patient: Yes.

DR. OSCHERWITZ: Is this the same aunt and uncle that you spent some time with early in your life?

Patient: Yes.

DR. OSCHERWITZ: My understanding is that you had asthma as a child.

Patient: Yes. I went to my grandmother's every year. I moved from Westchester to Long Island because the air was better.

DR. OSCHERWITZ: Starting at what age?

Patient: I don't know. I had it from the time I was 5 years old.

DR. OSCHERWITZ: I see. And then it was this aunt and uncle that you actually spent a few years with. Didn't you move in with them?

Patient: Not my uncle, just my aunt then, at my grandmother's house. They weren't married at that time.

DR. OSCHERWITZ: Now, when did your aunt and uncle come out here in relation to when you did? Did they precede you?

Patient: Ten years before me. They've been about 15 years here now.

DR. OSCHERWITZ: Is this something you've always had in the back of your mind? To come out on the West Coast, like they did?

Patient: Oh, yeah.

DR. OSCHERWITZ: Did you enjoy your first few years away from home?

Patient: Oh, I enjoyed it a lot. I was having a ball.

DR. OSCHERWITZ: What was it like?

Patient: Well, I was going out every night. I was on my own. Had my own responsibilities.

DR. OSCHERWITZ: And it seemed to go all right?

Patient: Yeah, it wasn't that difficult.

DR. OSCHERWITZ: Until your folks came out?

Patient: Until my folks came out.

DR. OSCHERWITZ: So what do you think's gonna happen if they come back out again now?

Patient: (No reply)

DR. OSCHERWITZ: You don't know?
Patient: I don't know.

DR. OSCHERWITZ: What have the major problems been for you in the last couple of months? You know, what's been worrying you the most?
Patient: Well, I'm just worried about going back to work. I wanta get back to work.

DR. OSCHERWITZ: What are your fears about it?
Patient: There are no fears about it.

DR. OSCHERWITZ: What are the worries?
Patient: No worries.

DR. OSCHERWITZ: No worries?
Patient: I just wanta go to work.

DR. OSCHERWITZ: Dr. Zeidman was describing a little about a time when you went back to work to get a tool and you thought you saw . . .
Patient (interrupting): Well, I thought I saw something, but it was probably only my subconscious mind.

DR. OSCHERWITZ: What do you think you saw? What do you recall?
Patient: I don't know. I went back for a tool.

DR. OSCHERWITZ: Yeah.
Patient: And what I saw was these fellows and girls going up on the second floor but see, I don't know . . .

DR. OSCHERWITZ: You don't know . . .
Patient: I don't know what transpired. I don't know what was going on.

DR. OSCHERWITZ: But the thought apparently was that the stewardesses were being prostitutes, is that it?
Patient: Something like that. Like I said, it was imagination.

DR. OSCHERWITZ: Was it an uncomfortable imagination?
Patient: Well, we got chewed out for being on the second floor in the first place. At least, I did. And I took it as an affront that I was the only one. And I wasn't. I mean, there was other guys going up there, too, but I was going up there for a specific reason.

DR. OSCHERWITZ: What was the reason?
Patient: I had to go move some stock around.

DR. OSCHERWITZ: What did the other guys go up for?
Patient: Why do I know? Ask them.

DR. OSCHERWITZ: What do you think? I'm sure you have a good imagination. Why might they go up? To be with the stewardesses?
Patient: I don't know. Could be.

DR. OSCHERWITZ: Had you been dating at that time?
Patient: Yeah, I was dating. I had a girl.

DR. OSCHERWITZ: How was it going with her?
Patient: It was fine, why?

DR. OSCHERWITZ: Good relationship?
Patient: Yes.

DR. OSCHERWITZ: Were you getting closer?
Patient: I was getting so close that I think I was knocking on that marriage door and I didn't want to knock on that door.

DR. OSCHERWITZ: Oh, really? That's pretty close, huh?
Patient: Yeah, that was pretty close.

DR. OSCHERWITZ: Why didn't you want to knock on that door?
Patient: Well, I don't know.

DR. OSCHERWITZ: When was that, that it was getting close?
Patient: Oh, a couple of years ago, I guess. Oh, you mean now? About six months ago.

DR. OSCHERWITZ: You still see her?
Patient: No. I'm down here and she's up there [in Los Angeles].

DR. OSCHERWITZ: How long had you known her?
Patient: Oh, about a year.

DR. OSCHERWITZ: She wanted to settle down?
Patient: She wanted to settle down, but I didn't want to.

DR. OSCHERWITZ: She wanted you to take care of her, huh?
Patient: Well, naturally.

DR. OSCHERWITZ: How old a gal?
Patient: Oh, about 33, 34.

DR. OSCHERWITZ: You were getting the jitters, huh?
Patient: Yeah, I was getting ready to move.

DR. OSCHERWITZ: You were going to move to get away from her?
Patient: Well, I always move, move from one apartment to another. I didn't really settle too long in one area.

DR. OSCHERWITZ: Was she in the same building?
Patient: Yeah, she was in my apartment.

DR. OSCHERWITZ: So you were gonna move to . . .
Patient: Greener pastures.

DR. OSCHERWITZ: Greener pastures, huh?
Patient: I don't know. I mighta, and I mighta not. I don't know.

DR. OSCHERWITZ: You mean you considered . . .
Patient: Before I cracked up. Yeah, I mean, I was thinking very serious about that.

DR. OSCHERWITZ: Would she have been a good woman for you?
Patient: I think so.

DR. OSCHERWITZ: Was your family aware that you were getting closer with a woman?
Patient: I don't know.

DR. OSCHERWITZ: Had you told your folks?
Patient: I told them about it.

DR. OSCHERWITZ: Were they happy about it?
Patient: Sure. My mother always wanted me to get married.

DR. OSCHERWITZ: She has?
Patient: Sure.

DR. OSCHERWITZ: She wants to cut your list?
Patient: Sure.

DR. OSCHERWITZ: Did that cause some nervousness?
Patient (with a slightly disinterested sigh): It might, I don't know.

DR. OSCHERWITZ: What else was going on in your life around the time that you've had these nervous troubles? There was the girl, and the folks and brother moving back and forth.
Patient: Well, they didn't move back and forth. He just caused a tremendous disturbance down here, and I got kicked out of the house down here and I had to go back to . . .

DR. OSCHERWITZ: Out of your folks' house?
Patient: Yeah.

DR. OSCHERWITZ: What was the disturbance that he caused?
Patient: I don't know. I had somethin' to do with something. I don't remember. But we had a big fight, and I left.

DR. OSCHERWITZ: Try to remember. What was this about?
Patient: Uh, I don't know. I told him to go and get a job, and he told me to go to hell, or something.

DR. OSCHERWITZ: Yeah, and then what happened?
Patient: So, he was gonna move out but my parents didn't want him to move out so they took the key away from me.

DR. OSCHERWITZ: They kicked you out?
Patient: I was kicked out.

DR. OSCHERWITZ: They figure you're able to take care of yourself and he isn't, is that it?
Patient: Well, I worked up in L.A; they lived down here. They expected me to come down every weekend.

DR. OSCHERWITZ: So they were expecting you down every weekend, and you were up there with the girl, she must have wanted you up there . . .
Patient: Yeah. Well, I stayed up there when I wanted to stay.

DR. OSCHERWITZ: Did she ever meet your folks?
Patient: No.

DR. OSCHERWITZ: Do you have any questions that you want to ask me about this meeting or about these microphones?
Patient: I'd like to know what they are all about.

DR. OSCHERWITZ: What do you think?
Patient (wryly): *Looks like a kangaroo court.*

DR. OSCHERWITZ: Yeah? What do you mean by a kangaroo court?
Patient: Looks like my verdict is already settled.

DR. OSCHERWITZ: What do you think it is?
Patient: I don't know. Judgment or what.

DR. OSCHERWITZ: What would you say?
Patient: Myself.

DR. OSCHERWITZ: A judgment of yourself? What do you think the verdict might be?
Patient: Guilty.

DR. OSCHERWITZ: Of what?
Patient: I don't know. (Lightly) *But it sure looks like a kangaroo court.*

DR. OSCHERWITZ: Yeah, it may look that way, but it isn't . . . Listen, we thank you for coming in. What we're trying to do is to understand, you know, what has happened. We're going to

try to understand it, and Dr. Zeidman will get back to you about it. I wish you good luck. Nice meeting you.

(The patient was escorted from the room.)

DR. ADDARIO:* Forty-three years ago an allergy specialist, Gordon Ailes, rediscovered and synthesized amphetamines, and the race to the drugstore and the local drug cache began. Amphetamine is efficacious in the treatment of narcolepsy and childhood hyperkinesia, and used widely as a diet medication. It is also the drug most sought and abused by people who want central nervous system stimulants. In 1938 Young and Scoville[1] first reported amphetamine psychosis in three narcoleptic patients. They felt that the psychosis was brought about by a state of increased alertness, and this theme reappears in much of the literature about amphetamine psychosis. Ideas of reference and misinterpretation of the environment apparently precipitated a paranoid psychosis in a patient whom they felt had latent paranoid tendencies but whom they thought would not have become psychotic if he had not used the drug. Arguments persist in attempts to construct a useful model, and we are still asking three basic questions: Can amphetamines precipitate schizophrenia? What neurochemical pathways, physiological mechanisms and personality features do schizophrenics and amphetamine users have in common? Are certain persons more susceptible than others to amphetamine psychosis? I am going to try to integrate what we think we know with the features of Hal's case.

The overall use of amphetamines is astonishing. Approximately 8 billion amphetamine tablets are produced in this country each year, half of which go into illegal markets.[2] That makes approximately 35 tablets (of 5 mg) for each man, woman and child in the country. The use, as you can imagine, is quite broad. For instance, 35 percent of all medical students use amphetamine at least once during their student careers. The use of drugs in general varies with age: men and women in their thirties are more likely to use stimulants; those in their forties and fifties are more likely to use tranquilizers; those in their sixties, sedatives. One would think it should be the other way around. Physicians play no small part in this, writing 31 million prescriptions for anorexics in 1967 alone. In spite of an intensive national campaign, by 1970 that number had been cut by less than 10 percent.

The countries that have had the broadest epidemics are Japan (from 1950 to 1956), Sweden (from 1964 to 1968) and the United States (from 1964 to 1969). Overall, about a tenth of the people who develop amphetamine psychosis remain chronically psychotic. Tatetsu[3] found, in a series of 500 cases, that 50 percent of the patients were in hospital less than six months, and 14 percent were there longer than five years. He felt that half of those 14 percent were schizophrenic. In Germany, Ladewig[4] found 22 cases of psychosis in a group of 64 amphetamine users. Of the 22 patients, 14 were in the hospital a week or less, presumably suffering from classic amphetamine psychosis; three were in the hospital one to six weeks; five for longer than six weeks.

There seems to be no relationship between the incidence of amphetamine psychosis and the duration or amount of drug use. People who have used as much as 300 mg daily for 15 years have not necessarily developed amphetamine psychosis. Others using small amounts over a shorter period of time have developed psychosis. Amphetamine psychosis has, therefore, occurred in all types of users, from the one time low-dose user to the chronic high-dose user.

There seem to be two types of amphetamine psychosis. The first type parallels the effects of alcohol or bromides or lysergic acid diethylamide (LSD). There's a lot of organicity. The sensorium is clouded. The patient is disoriented, bleary eyed, obviously spaced. The second type, the nontoxic type, which I think the patient today represents, mimics paranoid schizophrenia or a paranoid state, and is unrelated to dose level—whereas the toxic, fulminating type is usually related to extremely high doses in a single freakout.

Bell[5] has compared 14 cases of amphetamine psychosis with schizophrenia. In the first seven days they are virtually indistinguishable clinically. But then in amphetamine psychosis the paranoid delusions emerge well formed. These people are extremely sensitive to external stimuli; they do not manifest the classic schizophrenic thought disorder. Their associations are not loose or full of neologisms, nor are speech mechanisms with peculiar syntax present. They have a higher incidence of visual hallucinations than you might suspect. When you see a patient with visual hallucinations, consider an organic factor, a toxin of some type. In approximately 80 percent of Bell's

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14 cases of amphetamine psychosis, the patients had problems with visual miscueing, much like Hal has had. In nontoxic amphetamine psychosis the sensorium is clear. When I saw Hal in the emergency room, and when Dr. Zeidman saw him the next day, he was not loose; he related well, but he had these fixed visual hallucinations and delusional patterns in his cueing. The amphetamine psychotic has a guarded, aloof affect, not the flatness and anergy that you expect with schizophrenia. Amphetamine psychosis and amphetamine abuse usually carry with them heightened sexuality and stereotyped compulsive behavior. Phenothiazines are effective in treating both schizophrenia and amphetamine psychosis.

Now I would like to look at a biochemical model and see if we can stretch it far enough to connect it to a psychodynamic model. In 1972 Snyder[6] wrote a fine review of the biochemical literature dealing with amphetamines, claiming that amphetamine psychosis is perhaps the best experimental model of paranoid schizophrenia or the paranoid state that we have. In their chemical structure the catecholamines (epinephrine, norepinephrine and dopamine) differ little from amphetamines; except for a couple of small molecules they are basically the same. Amphetamines can mimic catecholamines and have been shown to have activity at the receptor site. They can inhibit the degradative enzyme monoamine oxidase. They can impair the reuptake of catecholamines by nerve endings. They also release catecholamines directly at the synapse. Therefore amphetamines increase the amounts of norepinephrine and dopamine at the synapse. Snyder describes how, using fluorescence histochemistry, Ungerstedt found separate neuroanatomical tracks for norepinephrine and dopamine in the brains of rats. The norepinephrine track seemed to be associated with alerting responses and locomotion and the dopamine track with stereotyped behavior. Carrying this reasoning to the human, Snyder speculates that the schizophrenic-like component of amphetamine psychosis may be mediated from the dopamine level, and the paranoid component facilitated from the norepinephrine level. Pharmacological and stereochemical evidence suggests that the clinical efficacy of phenothiazine drugs in schizophrenia is related to a blockade of dopamine receptors. Taken together these findings provoke speculation that amphetamines acting at dopamine and norepinephrine neurons may account for the major symptoms in the amphetamine psychosis.

Now I would like to look at some of the personality features of the amphetamine addict to see if they can be related to the biochemical findings. At Lexington, Ellinwood[7,8] found that 60 percent of the amphetamine addicts were of two types. Either they were schizoid or schizophrenic persons, or they were antisocial. He tried to find common features in these two groups, and he noted the process of internalization. Antisocial people seem to fail to internalize experience—they are constantly seeking out objects. They have very limited ability to form self images because they have not internalized their experience. And, child-like, they perpetually seek out stimuli; they want to move from one high to the next. Ellinwood felt that the amphetamines might produce a paradoxical calming effect in these people, as they do in hyperkinetic children, by stimulating internal arousal mechanisms and thereby reducing the need for environmental stimuli, and he saw the internal makeup of the schizoid personality as similar. He found also that the schizoid personalities had a greater tendency toward psychosis with the use of amphetamines. He found that these persons tended to be passive and described themselves as loners (as Hal did). They seemed to be sensitive. They felt inadequate and lethargic at times and were daydreamers with a lot of visual miscueing. Ellinwood felt these people sought amphetamine for its energizing and organizing effect on the ego, that it gave them an increased sense of internal arousal, internal awareness, a general sense of well being and a greater sense of self.

I will preface my remarks about Hal's case with a statement from a conference at the University of California at Los Angeles at which toxic and functional psychoses were compared: "No illness operates outside the psychic state and psychological background of the patient." All unresolved conflicts, guilts, and fears are activated and magnified by illness or stress. When we work with patients we too frequently look upon hallucinations or delusions simply as things we want to get rid of. It is important to realize that the distortions and delusions represent the particular coping mechanisms of that person, and allow him some function in the face of tremendous turmoil and inner chaos. Rather than get rid of these delusions and distortions we need to explore what they may mean symbolically to that person. If we reject them as simply "unreal" we're missing the boat.

Hal is 44 years old, and this is his first psychi-

atric illness. He seems a little old for the first onset of schizophrenia. He has a dramatic history of ingesting a toxin that can produce a psychosis we know is initially indistinguishable from schizophrenia. There are a number of schizoid features in his personality. He describes himself as a loner, and in his history and sibling relationships we notice deficits in his psychosexual development and his object relationships.

I feel that the foreman is an important figure here. Hal lived behind him, and his initial delusions dealt with the foreman's daughter. The amphetamines may have produced a homosexual panic. Because of the sexual turmoil, Hal may have misinterpreted his need for nurturing from the foreman. He remembers that when he was 19, his girlfriend died. He subsequently wrote what seemed to be an incestuous letter to his mother. I think that the death of that girlfriend is important and that it may represent a screen memory, specifically "recovery" of an experience to mask inner feelings. The death of the girlfriend may be connected to his sibling rivalry and a confusing wish that his brother had died. The incestuous letter strikes me as the attempt of a schizoid to return once again to the object relationship with the mother and gain from her. His return to the family after the hallucinations on the highway may be angry projections toward the family, and his involvement with the anonymous lady and the gun, and his view of the stewardesses as prostitutes, degraded objects, could be attempts to degrade the mother figure and assert his independence.

There is evidence of stereotypic behavior in his return to the scene of his arrest. It may be due to the amphetamines, but also it may be a message to us. I think that Hal, when he saw himself on the cross rising to heaven (which I interpret as a death phenomenon), ran back to be rearrested, seeking external controls when he felt he was becoming homicidal or suicidal. Too, we have to understand, in working with him, the issue of what drug taking means. Is it an attempt to become alive again? Is it a search for a new body image, a new sense of self, what?

In sum, I think we are dealing with a schizophreniform psychosis due to amphetamines in a person with a premorbid schizoid makeup. I think that Bell's clinical criteria are met: the delusions are paranoid and there is not much of an overt thinking disorder; the visual hallucinations are prominent and continual; his difficulties with object relationships are accentuated by the current stress.

DR. OSCHERWITZ: When there's a diagnostic problem involving possible psychotic illness I find it useful to take a careful developmental history to try to understand the organization of the coping mechanisms, the defenses the person is using to learn about the anxieties that are being fought against. Many theorists believe that what takes place in approximately the first three years in the development and growth of the infant and child reverberates throughout life, characterizing the kind of personality, the kind of coping mechanisms and the kind of conflicts that will develop in that person.

The most careful work on development that I have read has been by Margaret Mahler[9] who has distinguished normal sequential periods of separation and individuation in the first 36 months of life. She considers the first month to be normally *autistic*. Then a normal *symbiosis* between mother and infant lasts until the baby is about four months old. In the *differentiation* period between four and seven months the infant recognizes that there are other people besides himself; he becomes anxious with strangers and will cry when he sees a new face. Then there is a period of *practicing*. Mahler's description of practicing is very much like a description of manic or hypomanic behavior. She talks about the infant's love affair with the world. The child will run about on these newly walking legs and explore everything and be euphoric about everything he finds. The next period she calls *rapprochement:* the child will go out and recognize that he is by himself and then feel an urgent need to get back to his mother and cling to her. That goes on from 16 months until about 25 months. If things continue to go well the child achieves object constancy: the mother exists as an internal representation whether or not she is present. The child exists too, in his own right, in his own mind. This process is usually complete around 36 months.

Erik Erikson's work[10] on the development of identity is classic. He writes about the importance of developing trust instead of mistrust in the first year of life. Then he describes the achievement of autonomy instead of living with shame and self-doubt. Then the child either develops initiative or remains paralyzed by guilt. I am focusing on these early developmental tasks because we are discussing a patient who obviously has difficulties in

these areas. The psychic reverberations of borderline or psychotic patients usually come from poor personality integration in these early years.

The other theoretical concepts that I find particularly helpful here are those of Melanie Klein[11] and some of her successors, which deal with object relations. Interactions with parents, usually the mother, during the first 36 months of life have to do with loving and hating and whether the mother is able to maintain the loving relationship with the child. As this process unfolds, certain positions can be described. Klein recognized in infants feelings of disintegration, of fusing, of not even existing, and she described the anxiety these feelings of annihilation and persecution provoke, and the defenses used against them. If distrust develops—if, for instance, he is left unfed—a child is overwhelmed with rage, and in order to maintain the loving relationship with his mother he needs to separate the rage from her. So the first *position* a child assumes in order to cope is a *paranoid-schizoid* position. Klein thought that this happened within the first six months of life, but we know now that infants are not able to differentiate themselves from the people around them until approximately seven months of age, so although Klein's original timetable is probably incorrect, her clinical perception was very good.

Then, to deal with the anxiety that accompanies the realization of isolation and dependence on the mother, the child adopts a manic defense (comparable to Mahler's *practicing*), and this Klein called the *depressive* position. Third, it is hoped, comes *reparation:* love overcomes anger, and the child is able to move on from these primary relationships with the mother and father and siblings to relate with other people.

What happens if some of these developmental steps go awry? I think we see some of that in Hal. As Dr. Addario described, his delusions, his anxiety, have to do with destruction and persecution. It seems to me the central conflict for him is about dependency on his family. He was moved in and out of the home because of his asthma. We do not know much about the three other siblings, but he has an intense interaction with his younger brother. Moreover, the current question seems to be about his having a life with a woman on his own or going back into the family to go along with the whims of his parents and that controlling brother. I think his chronic underlying conflict is how to deal with his rage, and that is why the object relations theories are relevant here.

Let us consider a little more the coping mechanisms that people use to deal with their rage. Kernberg[12] writes about splitting other people into good or bad, because if one person is good *and* bad and if your rage is greater than your love, then that person cannot exist for you. Or the split can be between the external environment (and the people in it) and the internal. Hal projected aggression onto the trees; he had to use relatively inanimate objects; he could not find a person whom he was willing to delegate the rage to. That is why I asked him who he was trying to protect the aunt and uncle against. His splitting of the rage to an inanimate object is a primitive maneuver; we see that in very young children. Sometimes, when the boundaries of the self are unclear, rage is projected onto the environment and other people, but the love is kept to the self. It is just a different kind of split, separating the rage from the love so that other people can exist and so that the person himself can exist.

I think that when Hal was having his most intense anxiety he was in the first position, at the level of annihilation and fusion and persecution anxiety. Did he exist as a human being or not? He was not depressed or guilty. To be in the depressive position you have to be aware that you need and want the person (mother) and at times cannot have her, and that you love and hate her at different times. I think Hal regressed to an earlier level than that. This may explain why, with time, there was a higher depressive score on the MMPI. At least I hope that he was moving from the schizoid fears of annihilation to a more clear awareness that there are other people around him, and that he is angry with them, and that his anger does not destroy them.

The specific diagnosis is not a problem for me because I assume that several things are operating: a toxic element and the developmental difficulty and a chronic schizoid personality. I do not see any reason to try to determine which one it is; it is usually a matter of which one is in ascendancy, but there is always a combination of factors.

DR. NEMIROFF:* The case presentation and discussion have made this patient's problems with separation and individuation very clear for me. Wieder and Kaplan[13] have tried to learn why people use particular drugs, how the effects of certain drugs mesh with individual needs. They

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studied people who use LSD or marijuana or heroin or amphetamines as well as people in treatment of various sorts. They suggest that people who choose amphetamines seem to be fixated in this separation-individuation conflict. The drug gives them a sense of alertness and competence. "I don't need anybody; I can do it myself." This patient too struggles with an overwhelming sense of inadequacy and incompetence, the fear that he cannot make it, that he is nothing—zero. The drug must have provided the illusion that he could cope better.

DR. ADDARIO: Hal's life is in a shambles right now. He is discredited by his foreman in Los Angeles; he has been admitted to hospital for psychiatric reasons; legal charges hang over his head. Sometimes stress can damage an ego so badly that it does not reconstitute even though a significant precipitating factor (in his case the amphetamines) has been removed.

DR. ZEIDMAN: The court ruled him not guilty of the crime by reason of insanity at the time the crime was allegedly committed. But if he were to be insane at the time of the judgment, state law would require that he be sent to a state hospital for 90 days, despite what any psychiatrists say, despite what the judge would like to do, despite what the prosecuting attorney would like to do. Now sentencing has been posponed 90 days. If a court-appointed psychiatrist can say he is no longer insane then, he would be cleared of the charges and would not have to enter a hospital. If that does not happen perhaps he could be admitted to a Veterans Administration hospital in lieu of the state hospital.

DR. OSCHERWITZ: There are therapeutic implications in what we have said. Hal seemed to be on the threshold of being able to make a life on his own with a woman, away from his parents and brother. He felt a great deal of conflict about that, and it turned out that he took a regressive step. This man needs a good deal of buffering from his family and some help in seeking independence. His first comment, "I just want to go to work," gave me the impression that he still uses a good deal of denial. I would guess he behaved this way before his illness. At this point I might describe his personality as schizoid, but it seems like the psychosis is in remission. I hope it is. If I had pressed maybe we would have found that it is not in remission, but I had the feeling that it is. I thought it was a good prognostic sign that he said maybe he should have stayed with that woman. At first his idea was to get away, and then he had some doubt about that. I think that doubt could be worked with.

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Recent Chapters in the Factor VIII Saga—Perils of a Protein

Fifth Annual Paul M. Aggeler Memorial Lecture

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Assistant Professor of Medicine, and H. David Watts, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, CA 94143.

DR. POOL:* It is routine to speak of the honor involved in delivering a memorial lecture, and it is routine to speak of those who are no longer with us in terms of respect and admiration which might never have seemed appropriate during their lifetimes. But I want to claim the non-routine distinction of having felt that way about Paul Aggeler while he was still alive.

Although I met Paul in 1953 soon after I entered the field of blood coagulation at Stanford, my contacts with him for a number of years were not frequent enough to produce more than two strong impressions: one, his remarkable intellectual grasp of this field which had produced his breakthrough discovery of plasma thromboplastin component (PTC); and two, his extraordinary modesty about his accomplishments. But late in 1968, less than a year before Paul died, we were both asked to serve on the same site-visit team to an institution on the East Coast. We flew from San Francisco to Washington together and, after a couple of days of meetings there, flew back again. There were about nine or ten hours of conversation on these airplanes which produced in me a kind of awed response which, as I mentioned above, we usually reserve for people who have already died. It was not just Paul's extraordinary sense of understanding and acceptance for all the colleagues and associates we were discussing, but the fact that the highest standards for conduct were the continual background against which people were viewed. A saint-like figure might take pride in turning cheek after cheek to shortcomings and misdemeanors, but one would not care to make him responsible for medical training. On the other hand, a rigid taskmaster who is aware only of his need for perfect performance by his subordinates is a relatively common figure in medical education. The rarity, and it was one of my most privileged experiences to be exposed to one, is a person who applies the highest standards, but applies them to a *human* being, not to a paper

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cutout, and then makes a humane judgment—not self-serving, but wise. Such a person was Paul Aggeler, and one knew it while he was still alive.

Since hemophilia was one of Paul's primary interests, and since it is the only scientific field I know anything about, I thought I would try to create a bird's-eye view of it this morning. I do so fully aware that this is almost certainly not the best moment in time to make that attempt, at least with regard to the molecular mysteries of hemophilia. My estimate is that a Paul M. Aggeler Memorial Lecturer a few years from today will be able to put nearly all of the pieces of the jigsaw puzzle into place for you, and I envy him or her that experience. Right now we are all plagued by conflicting answers to the major questions and a paucity of critical experiments which would permit a sound choice.

A Deficiency Disease

We do have some things to be pleased about, however. Perhaps you already know that hemophilia was identified as a deficiency disease about 60 years ago when Tom Addis at Stanford showed that the long clotting time of hemophilic blood could be shortened by the addition of a very small amount of normal blood. Dr. Addis' name is not prominent in the history of hemophilia research simply because he assumed the missing factor was prothrombin; he made that error because at that time only prothrombin and fibrinogen had been identified as clotting factors in blood. Since the hemophilic patient's blood did eventually clot, it followed that he had fibrinogen; the deduction of Dr. Addis was that the blood, therefore, lacked prothrombin. In the ensuing years, not only has it been shown that hemophilia results from deficiency of a third factor, but it has also been shown that coagulation of normal blood requires the participation of approximately nine different proteins, deficiency of any one of which is associated with a clotting disorder. Hemophilia, however, is by far the most common of these deficiency disorders, probably accounting for 80 percent; next in frequency is PTC deficiency, the one identified by Paul Aggeler and his associates and which accounts for another 15 percent. Together the other seven deficiency states account for the remaining 5 percent. Figure 1, illustrating our present concept of the intrinsic and extrinsic blood clotting cascades, reminds you that the antihemophilic globulin, now usually called Factor VIII, functions in approximately the middle of the intrinsic system, with PTC, now usually called Factor IX, immediately preceding it.

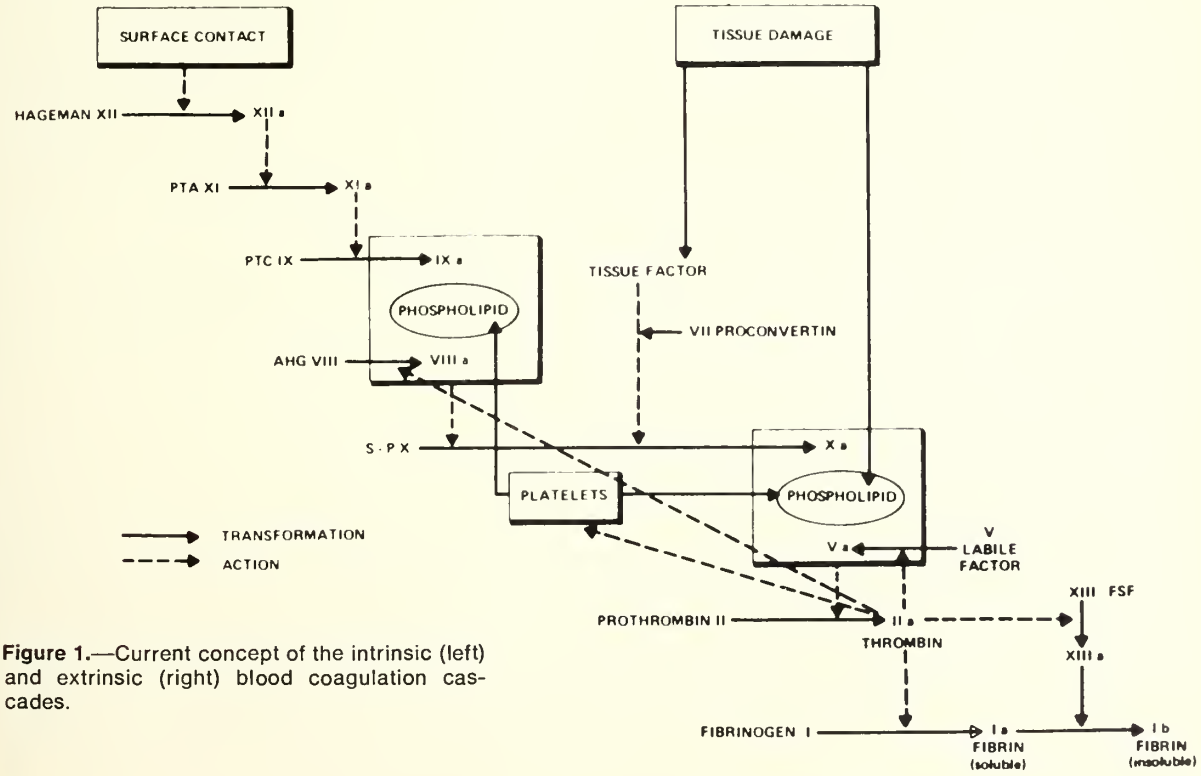

Figure 1.—Current concept of the intrinsic (left) and extrinsic (right) blood coagulation cascades.

Replacement Therapy

Identification of hemophilia as a deficiency disorder was naturally followed by attempts at replacement therapy in patients. Early experiences with whole blood, and then plasma, although occasionally successful, were frustrated by the complication of circulatory overload which accompanied most attempts to raise sufficiently the blood level of Factor VIII—and the lability of this protein during storage greatly exacerbated the problem. Therefore, in the late forties and early fifties there began a search for a concentrated form of antihemophilic globulin which could be safely infused to raise the circulating Factor VIII to about the 25 percent level to stop promptly all but the smallest hemorrhages and to about 50 percent in order to support major surgical procedures.

This goal has now been accomplished, and for the past ten years physicians caring for hemophilic patients have luxuriated in the availability of concentrated Factor VIII for therapy. There are two sets of reasons, however, why those of us involved in this field have nevertheless not been able to fold up our laboratories and retire to other concerns. One set has to do with the actual supply and delivery of concentrated Factor VIII to the patients needing it; and the other set has to do with remaining urgent problems for this group of patients—such as prevention of the birth of hemophilic children in families having the disease, and management of those patients in whom an inhibitor antibody to Factor VIII develops.

The English Experience

To discuss first the problem of supply of Factor VIII concentrates for hemophilic patients, I would like to share some of the thoughts which resulted from having spent this past year at the Oxford Haemophilia Centre in England. As you all know, England is operating with a National Health Service and has had 26 years of experience with it. The way in which a chronic disease like hemophilia is managed under such a service could perhaps be instructive for us in our forthcoming adaptation to similar conditions.

Figure 2.—Hemophilic patient carrying out his own venipuncture.

Perhaps the problem should be described as "research success." By this I mean that as long as the only therapy which could be offered was transfusion of plasma or blood, the way seemed clear. Bleeding patients were admitted to the hospital, but the volume of transfusions and, correspondingly, the benefit received was severely limited. However, now that research has made concentrates of Factor VIII available, the potential for far greater benefit, but unfortunately also for far greater costs in both money and starting plasma, has expanded for this group of patients. Major surgical procedures, including corrective orthopedic operations for deformities caused by previous, inadequate therapy of the disease, are now everyday events; and the finishing touch to the new era has been the recent introduction of home therapy.

At many centers around the world, boys as young as 10 years of age have been taught to self-administer Factor VIII as soon as they are aware that a hemorrhage has begun. Figure 2 shows a teenager carrying out his own venipuncture. Parents are trained to do infusions for younger children. The impact of this program has been almost too great to convey. There is a euphoria of independence in many of the patients, but it is not just subjective enthusiasm; there are hard data to show that the decreases in school and job absenteeism and in morbidity are truly dramatic. There is a problem, though: What is to be the source of the necessary concentrated Factor VIII?

National Health Service

There is a basic similarity between this question and the one raised by other chronic diseases for which expensive therapy can be available to certain groups of patients if the balance of the population is willing to pay for it. But in the case of hemophilia adequate supplies of starting material, that is plasma, is an additional problem. How are these problems handled in the setting of the Na-

tional Health Service? I cannot claim to have expert knowledge on this question but, watching as a lay observer, one could see that England lags behind, for example, the United States, Germany and Italy, in instituting home therapy and providing elective surgical procedures. There is very significant delay in all but emergency care throughout the Health Service, for lack of facilities in general, and for lack of Factor VIII concentrate in the particular case of hemophilia.

Why is the supply inadequate and what can be done about it? I suggest that the reason is the laissez-faire atmosphere in which British blood banks function; and the solution, therefore, is a tighter link between the needs of blood component users and the output of the blood bankers. Historically, they, as well as blood banks in this country, have been oriented primarily toward having units of whole blood available on demand for surgical operations and trauma patients; but components prepared from blood are viewed by many banks as an extra burden to be undertaken only if convenient.

The Factor VIII story is further complicated, however, by the fact that there are two general types of concentrates—and their characteristics, costs and potential supplies are different. A choice exists between a simple concentrate which can be made in local blood banks in such a way that the balance of the donated blood can be immediately reconstituted for use in ordinary transfusions and the somewhat sophisticated preparations which result from further chemical fractionation of the same type of starting material. A comparison between the characteristics of these two preparations is shown in Table 1. The simple concentrates, known as cryoprecipitates, are prepared from individual donations of blood, whereas the alternative, pharmaceutical preparations in the United States are prepared from very large plasma pools of 1,000 liters, which have been collected from as many as 3,000 paid donors by plasmapheresis.

At the Oxford Haemophilia Centre there is a small fractionation laboratory which makes an excellent freeze-dried concentrate, but uses a starting volume of only 100 liters. Such small volume processes would be impractical in the United States because government testing requirements for sterility, pyrogens and potency are such that a significant fraction of each batch would be used up. However, in the United Kingdom only government laboratories are permitted to fractionate blood, and therefore the regulations can be set by another arm of the same body. Although the yield in a small batch process may be quite good, when the process is carried out on a 1,000-liter scale the yield is approximately one third as much. This is one of the major reasons for the much higher price, with expenses for extra processing, marketing, research and development, profit, and the like, also contributing. Although we know the actual cost of making the blood bank product, we of course do not have that information for the commercial preparation and no one has attempted to calculate it for the preparation in Oxford, where a whole building and a large staff are dedicated to its production.

Apart from cost, there are advantages and disadvantages to the final products. The advantages of cryoprecipitate include the lower hepatitis risk because of the smaller pool size and the possibility of administration on a type-specific basis where that seems advisable. The disadvantages of cryoprecipitate vis-a-vis pharmaceutical concentrates are the requirement for freezer storage instead of refrigerator, and the unpredictability of the precise potency of any given package.

Needs in a Given Population

Let us consider now what the needs for these materials might be in a given population and how those needs may best be met. In 1972 the National Blood Resource Program of the National Institutes of Health made an intensive study of hemophilia in the United States in order to evaluate this problem. This study showed that there are close to 20,000 patients in the United States with a sufficiently severe form of hemophilia to require trans-

TABLE 1.—*Comparison Among Three Factor VIII Concentrates*

Source	*Yield (percent)*	*Cost/Price Per Unit Factor VIII*	*Storage*	*Isoantibodies*	*Potency Data*
Cryoprecipitates (Individual volunteer donor)	50	2.0¢/6.5¢	−20°C	0	estimate
USA Pharmaceutical Concentrates (Pool of >1,000 paid donors)	15	?/13¢ USA ?/25¢ U.K.	4°C	+++	precise
UK-Oxford Freeze-dried Concentrate (Pool of ca. 400 volunteer donors)	40	?/Free	4°C	?	precise

fusion at least once during a given year. The amount of Factor VIII which the average patient needs in the course of a year was also estimated, and from these two figures the projected demand was determined.

Table 2 presents certain conclusions drawn from the data: If a process with 50 percent yield is used, the Factor VIII from just under 3,000,000 units of donated blood would be required to meet the national demand; but if dry concentrates are used, almost 10,000,000 units of whole blood would be required as the source material. These figures are for a program of episodic transfusion which occurs as a result of a patient's detecting the beginning of a hemorrhage. If a program of prophylaxis is attempted in which every 48 hours infusions are administered, these figures become astronomical—relative to the baseline value of 7.6 million units of whole blood which were collected from volunteer donors in this country during 1971. Although another 2.5 million units of whole blood and plasma were collected from commercial donors and all pharmaceutical Factor VIII is made from this source, it should be realized that the goal of a totally volunteer blood donor system has recently been adopted by both the Department of Health, Education, and Welfare (HEW) and the noncommercial participants in the American blood complex. This objective is the only one compatible with both control of serum hepatitis and ethical standards which make unacceptable the concept of bleeding poor people for transfusions of the rich.

Fortunately, there is no convincing argument for the goals of universal prophylactic therapy because, as all workers with hemophilic patients know, these patients have variable and sometimes lengthy periods with no bleeding episodes at all. Prophylaxis is therefore advisable only during those short periods when there is a greatly exacerbated tendency to bleed, and such periods do occur for reasons that none of us understands. On the other hand, the goal of prompt home treatment for every hemorrhage in its earliest stage, is one which is now universally agreed upon, and this could be achieved in this country if about half to two thirds of the blood now being collected from volunteers has its Factor VIII extracted in blood banks; whereas even the total volunteer blood supply would not provide enough Factor VIII via low-yield processes. The HEW study did not provide data on how close we are currently coming to meeting the needs of the nation's hemophilic patients, but it is likely that a considerable gap still exists between needs and supplies, especially in some areas. This is one of the strong arguments for establishing an integrated national system so that overall need determines production—and shipment into heavy use areas is made by those banks with few patients to provide for.

TABLE 2.—*Potential Demand by Hemophiliacs for Blood Products (United States)*

Units of Whole Blood Required to Produce:	
Episodic Infusion	
Cryoprecipitates	2,939,000
Dry Concentrates	9,796,000
Prophylactic Infusion	
Cryoprecipitates	13,344,000
Dry Concentrates	44,435,520
Whole Blood Collected by Volunteer Blood Banks during 1971	7,618,000 units

Special Conditions in England

To return now to the special conditions in England: there has been a chronic and fairly severe shortage of Factor VIII concentrates since their earliest development in that country. The nation as a whole depends primarily on cryoprecipitates for use in its 40-odd hemophilia centers. However, the Oxford area is special since its center not only is the largest one but also the only one with a fractionation laboratory that can turn out a large part of the Factor VIII needed by this center and that could turn out more if it had more plasma to process. However, it could not hope to supply other centers.[1]

What happens in such a shortage economy? Without any doubt, hemorrhages are treated if a bleeding patient arrives at a hospital or hemophilia center. The unsatisfied demand consists of patients waiting for corrective surgical procedures and those who might—as a result of having home therapy available—benefit to the point of living approximately normal lives for the first time. The stocking of home stores with concentrated Factor VIII is far beyond the present capability of the English system. One of the special considerations here is that the home freezer is not as common a piece of equipment in that country as it is in ours; thus, either patients would have to be supplied with freezers if they were to store wet-frozen cryoprecipitates, or they would have to be given dry concentrates which can tolerate 4°C (39°F) storage.

There is currently a developing outcry, as you

may have been reading in *Lancet,* for a greatly increased supply of dry concentrates. Such could be provided if the government established many other minifractionation plants all over the country and was able to populate them with experienced and dedicated staff like those in Oxford. Alternatively, it seemed to this visitor that some of the autonomy could be removed from the blood banks so that they were not so free to decide whether or not they cared to make enough cryoprecipitates to meet the demand and whether or not they wished to meet quality control standards for their product. The blood bank solution to the problem would have the advantages of far lower cost and a far easier national adjustment than arranging for all those same recalcitrant blood banks to remove the plasma from most of their collected blood, quick-freeze and ship it to the nearest fractionation plant, and then persuade local practicing physicians to switch to packed red cells for their transfusions. The disadvantage of the blood bank solution would be the need to provide small freezers for home therapy patients.

Practicing Physicians

How do the practicing physicians cope in the interim? This is perhaps the point at which the "crunch" occurs. And it has occurred because in 1973 the National Health Service licensed the sale of an American commercial concentrate of Factor VIII. Of course this means that United States commercial donors willing to be plasmapheresed are now providing Factor VIII for British as well as American hemophilic patients. It also means a new dilemma in Britain: Now that the outside product, along with its exceedingly high price, has been licensed, what is to prevent hemophilia centers from ordering as much of this material as they think appropriate for optimum medical care of their patients? Although in the past there has been an allocation of a particular budget for pharmaceuticals to each medical installation, no one has faced up to the issue of whether it is justified for a physician to withhold such materials when they are actually available but he has exceeded his budget. The next few months will see the resolution of this question with regard to the hemophilia problem, because many hemophilia center directors are proceeding according to the dictates of their conscience and are ordering such materials often at a great excess in cost over their allocated budgets. It remains to be seen how the financial officers for the National Health Service will react to this development.

It provokes speculation in a visitor, however, with regard to such problems, which no doubt will soon be rampant on this side of the Atlantic—if they are not already. Even now we have a situation in which 13 states have special legislation covering costs of care and concentrates for hemophilia patients. Should every patient have an equal right to "go deluxe" with high priced pharmaceutical concentrates stored at home in ample quantity? It is true that even this program would in the long run cost less than the frequent admissions to hospital, the crippling and the failure of self-support which may be the consequences of inadequate therapy.

My own editorial commentary is as follows: Even if a national health service or a local state law provided seemingly unlimited resources, it would be a mistake to be wasteful. Any group runs the risk of blacklash stringency once it has been revealed that what was wasted by one group may have been desperately needed by another. In my view, it must be considered wrong to use a 15-percent yield process if a 50-percent one will do; to use commercial donors if the volunteer supply will do; to use prophylactic therapy if episodic infusions will do.

Controversies in Hemophilia Research

I would like now to turn to a sketch of some current controversies in hemophilia research in order to provide a background against which you can watch future developments.

The central issue is certainly the molecular nature of the defect in this disease. We still do not know very much about the normal Factor VIII molecule; and we also do not know whether an incompetent molecule is synthesized in hemophilia or whether there is a total failure to synthesize anything resembling Factor VIII. This latter question is important because the answers to two urgent problems seem to rest on this issue or close to it. The problems are the cause of the inhibitor antibody which forms in 10 percent of hemophilic patients and the diagnosis of the carrier state.

Until 1972, we all operated on the assumption that classic hemophilia was the result of deficient synthesis of Factor VIII by a tissue not yet identified but most likely part of the reticuloendothelial system, and that mild cases of hemophilia were the result of a mild deficiency of such synthesis. It had been well established, of course, that the

genetic defect was carried on the X chromosome, and the casual assumption was made that incorrect coding of a single structural gene with consequent aborting of synthesis was responsible for the disease. Brushed under the rug was the uncomfortable question as to how a continuous series of circulating Factor VIII levels, from the less than 1 percent of the mean value found in severe hemophilic patients to the 200 percent levels found at the top of the normal range, could be controlled by a single genetic locus. Even more challenging was the realization in the 1950's that another disease, von Willebrand's disease, resulted in a characteristically low level of circulating Factor VIII. Von Willebrand's disease is characterized by the combination of low Factor VIII and a prolonged bleeding time, the latter probably owing to a deficiency of a second plasma protein.[2] At this point, then, we can no longer pretend that a single gene hypothesis for control of Factor VIII level is tenable. The geneticists interested in this problem are not yet prepared to propose an alternative hypothesis which accounts for all the available data.

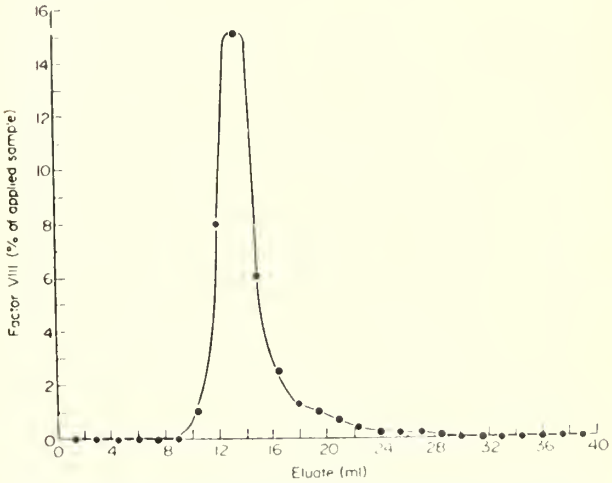

Chart 1.—Factor VIII activity in gel filtration samples of normal unreacted Factor VIII. (From Austen DEG: Br J Haematol 27:89-100, 1974)

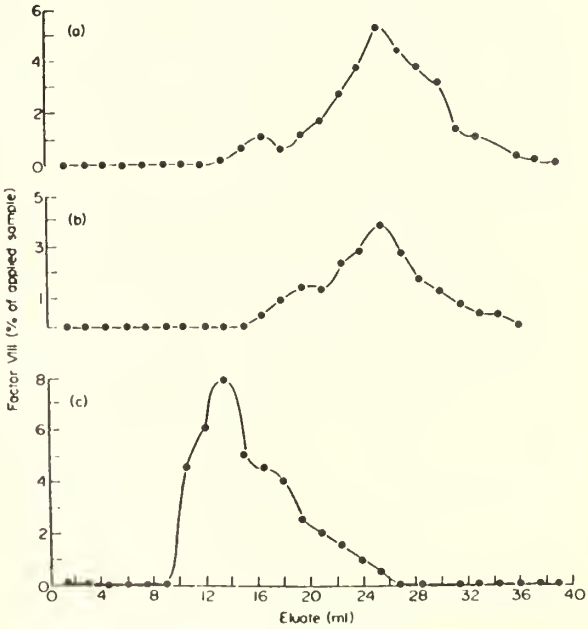

Chart 2.—Human Factor VIII activity in gel filtration samples: (a) Human Factor VIII of small molecular weight produced by reaction with dithiothreitol. (b) Activity peak seen in panel (a) subjected to gel filtration for a second time. (c) Aggregated Factor VIII produced by aminocaproic acid reaction. (From Austen DEG: Br J Haematol 27:89-100, 1974)

Biochemistry of Factor VIII

Let us take a look at what we do know about the biochemistry of Factor VIII and then see where are the gaps in our knowledge. Only within the last four years has it become clear that we are dealing with what is possibly the largest molecule in our circulations; an entity with a molecular weight in the 1 to 2 million range. As you might imagine, when this kind of data appeared during column chromatography of purified Factor VIII preparations, it was considered likely that such a large molecule was not a unique polypeptide chain but rather a polymer of much smaller chains. About two years ago, the group in Chapel Hill succeeded in depolymerizing this molecule with methods sufficiently gentle that the Factor VIII clotting activity was preserved. We now know that either high salt concentrations or mild reducing agents are able to separate the large polymer into monomers of approximately 200,000 molecular weight. Chart 1 shows results of an experiment of this kind conducted in Oxford by Dr. Denis Austen. Using a Factor VIII clotting assay, he too found that the activity of a Factor VIII concentrate eluted entirely in the void volume of a column of Sephadex G200. But after that fraction was treated with dithiothreitol (DTT), a mild reducing agent, the activity eluted in a much later fraction, with the proteins of 200,000 molecular weight (Chart 2). A recycling through the column confirmed that this molecule was still in a small molecular weight fraction, but dialysis to remove the DTT, plus addition of epsilon aminocaproic acid, for a function not yet defined, allowed repolymerization of the molecule so that Factor VIII activity once again eluted in the void volume.

Now, why is not this neat picture the whole story?

Historically, the reason is that, in parallel with investigation like those just described, other laboratories were searching for immunological identification of Factor VIII in the hope that detection of a dummy molecule in hemophilia would open the way to both carrier detection and an explanation for inhibitor development.

Dramatic Breakthrough?

In 1972 a dramatic breakthrough in this effort appeared to emerge from Dr. Ratnoff's laboratory in Cleveland; Dr. Ratnoff himself reviewed these findings during his Paul Aggeler Memorial Lecture one year ago. I think it is a fair summary to say that although the precise picture delineated by Dr. Ratnoff's group over the past couple of years is probably not correct, there is nevertheless important significance to his findings.

Dr. Ratnoff and his colleague, Dr. Zimmerman, were dealing with the fact that the inhibitor antibody which develops in hemophilic patients had never shown a precipitin reaction with Factor VIII no matter what concentrations or conditions for the reactants were used.

What could the explanation for this failure of precipitation be? One hypothesis often considered was that although Factor VIII is a large molecule, its functional enzymatic group is only a small area of that molecule. It seemed possible that patients in whom antibody is produced might have nonfunctional Factor VIII, the bulk of which was normal in structure but the small functional area of which was sufficiently abnormal to be antigenic. If that were the case, one would expect transfusions of hemophilic patients with normal Factor VIII to stimulate antibody specific for that active site alone. It would then follow that although the antibody formed was typical bivalent immunoglobulin G (IgG), the Factor VIII with which the antibody reacted would be monovalent, having only one antigenic site per molecule and this would, of course, preclude the lattice formation which is essential for precipitation.

TABLE 3.—*Immunology of Classic Hemophilia and von Willebrand's Disease (Ratnoff Hypothesis)*

	Functional Activity (percent)	*"Antigenic" Activity (percent)*
Normal	100	100
Severe Classic Hemophilia	0	100
Carrier of Hemophilia	50	100
von Willebrand's Disease	20	20

Building on this concept, it was reasonable to suppose that if one used a heterologous source instead of the human antibody to Factor VIII, the active enzymatic site would not be the only antigenic determinant in the recipient. Although rabbits, for example, do have Factor VIII which is fully able to substitute for human Factor VIII in a clotting system, one would nevertheless imagine that human Factor VIII might provoke the formation of antibody with several different specificities in this animal; the antigen would then be multivalent with respect to these antibodies and precipitation with consequent immuno-identification should then be possible.

This was the approach which Dr. Ratnoff took. Rabbits were stimulated to produce high-titer anti-Factor VIII antiserum by injection with partially purified human Factor VIII, since even our very best preparations are only partially purified. This antiserum produced several precipitin lines when reacted with human Factor VIII concentrates in Ouchterlony gel plates. The hope was, of course, that one of these lines was the Factor VIII-anti-Factor VIII line and the rabbit antiserum was absorbed with Factor VIII-free fractions of human plasma until all but one of the lines were removed. Since the absorbed antiserum was still capable of inhibiting the biological activity of Factor VIII in a clotting test, the tempting deduction was made: That the single gel line was the long sought evidence of immunoprecipitation of Factor VIII by antibody. With such an exciting tool, it is no wonder that a wealth of experimental observations from many laboratories followed.

The Laurell technique for quantitative immunoelectrophoresis was used to assay "Factor VIII antigen" in many samples of plasma and these values were compared with the quantity of clotting factor as determined by coagulation assays on the same plasmas. The conclusions, shown in Table 3, were that normal persons have corresponding levels of clotting factor and antigen; that hemophilic patients who have zero levels of clotting factor have either normal or elevated levels of antigen; that carriers of hemophilia have roughly twice as much antigen as they have clotting factor, and that von Willebrand patients have low levels of both antigen and clotting factor. These observations led very naturally to the proposal that the normal Factor VIII molecule is bifunctional, possessing both a clotting function and a platelet adhesiveness function, the latter identified by rabbit antibody; that hemophilia is

TABLE 4.—*Differing Partition of Factor VIII Clotting Activity and Antigen Detected by Rabbit Antisera to "Factor VIII" Between Cryoprecipitate and Supernatant Plasma (From Hougie C, Sargeant R: Lancet I:616-617, Mar 17, 1973)*

	Antigen	*Factor VIII*
Plasma	100	100
Cryoprecipitate	98	64
Supernatant	<3	36

associated with a hemi-functional molecule capable of supporting platelet adhesiveness but not coagulation; that von Willebrand's disease is associated with deficient production of a normal Factor VIII molecule, and that the carrier could be detected by Lyon-determined production of part normal and part hemi-functional Factor VIII.

In fact, the first disturbing observations for this very attractive hypothesis came from the same laboratory which produced the data just described. These were pronounced discrepancies between the observed half-life for antigen and that for clotting activity following transfusion of von Willebrand and hemophilic patients.

Recent Reports

A number of more recent reports now raise strong doubt that the immuno-assay and the clotting assay are identifying the same entity. Table 4 presents data reported by Hougie and Sargeant showing that when simple cryoprecipitation of plasma is carried out, a significant part of the clotting activity remains in the supernatant, but essentially all of the detectable antigen is recovered in the precipitate. The observations in Chart 3 come from the same Dr. Zimmerman who worked with Dr. Ratnoff on the early experiments, now in La Jolla collaborating with Dr. Edgington. They found that when the human antibody to Factor VIII, almost surely specific for the clotting site, is insolubilized by binding to Sepharose beads, plasma passed over a column of these beads loses much of its Factor VIII activity but almost none of its antigenic activity.[3]

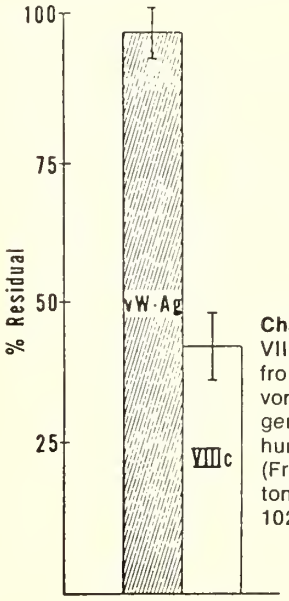

Chart 3.—Removal of Factor VIII coagulant activity (VIII) from plasma, independent of von Willebrand's disease antigen[c] (vW-Ag), by insolubilized human isoantibodies to VIII. (From Zimmerman TS, Edgington TS: J Exp Med 138:1015-1020, 1973)

Finally, a whole series of workers have shown that when Factor VIII preparations are depolymerized by the treatments we have described and then chromatographed, the clotting activity elutes in small molecular weight fractions but the rabbit antibody-identified antigen is still recovered as a high molecular weight component in the void volume. At this point we cannot say whether these findings result from the fact that the two activities are entirely separate molecules or that they are two molecules of a complex which is easily dissociated by physical means such as cryoprecipitation or gravity-flow; but we must face the fact that no incontrovertible evidence is yet available for the immuno-identification of the Factor VIII molecule.

Is there any way in which we can put all these observations together and, having done so, cast light on our urgent problems? The answer is, probably not, but we can begin the job.

Two Views of the Factor VIII Molecule

Figure 3 shows the two most popular current versions of the Factor VIII molecule, both of which can be considered largely, but not entirely, consistent with the data we now have. Obviously, it is not yet possible to make a definitive choice between them. On the one hand, Factor VIII may be a complex protein containing a large molecular weight portion loosely bound to a much smaller one; this concept would locate the clotting activity on the small fragment of about 200,000 molecular weight and the antigen identified by rabbit antisera on the larger portion. One can continue to speculate that this large portion carries the von Willebrand activity required for normal bleeding times. Depolymerization, then, would allow the small fragments to come out in later fractions but leave the large molecular weight portion in the void volume.

Alternatively, many investigators feel that the more likely hypothesis is the one shown at the bottom of the figure, which suggests that Factor

VIII is a polymer consisting of 200,000 molecular weight monomers, each of which has Factor VIII activity but no immunologically identifiable antigen activity. This version would require that the von Willebrand factor be considered a separate protein having approximately the same molecular size as the Factor VIII but identified by its effect on platelet adhesiveness and by rabbit antibodies to purified preparations of it.

What are the critical arguments for and against each of these versions and how do these concepts relate to our practical problems? The principal impediment to acceptance of the upper picture is the ready separation of the two entities by purely physical maneuvers. If the attachment is so loose, can we be talking about one molecule? Suppose the attachment is so loose that it is equivalent to the albumin-binding that occurs with many other passengers in plasma? I would propose that if the binding is that kind of almost accidental association, then measurement of this antigen will tell us no more about the concentration of Factor VIII molecules than measuring albumin would tell us about the concentration of bilirubin. A second critical argument against the upper sketch is Dr. Austen's success in repolymerizing a presumably pure small molecular weight fraction into exclusion volume material, as depicted in Chart 2.

How about the lower sketch? I believe the only firm attack on this version of the Factor VIII molecule consists of the following reported data: a close correlation between the values for antigen and clotting activities in normal persons, parallel changes in the two values during stress and pregnancy and frequently successful identification of carriers by higher-than-normal ratios of antigen to clotting activities.

Carriers, as a group, have lower Factor VIII levels than normal women, but both groups have a sufficiently wide range, with a sufficiently broad overlap, that simple measurement of a potential carrier's Factor VIII does not necessarily inform us as to her status. There is certainly an urgent need for a refinement of this index.

If the Factor VIII antigen assay is measuring not a part of the Factor VIII molecule, but the von Willebrand protein contaminant of the Factor VIII preparation used to immunize rabbits, then it would naturally follow that this protein was present in normal quantities in hemophilic patients, and probably in carriers as well. If it is a quite separate factor, it follows that comparing its level to that of clotting Factor VIII in potential carrier patients would have no more significance than comparing the Factor VIII in these patients with their fibrinogen, for instance, the level of which also rises during stress and pregnancy.

Since some laboratories have not been success-

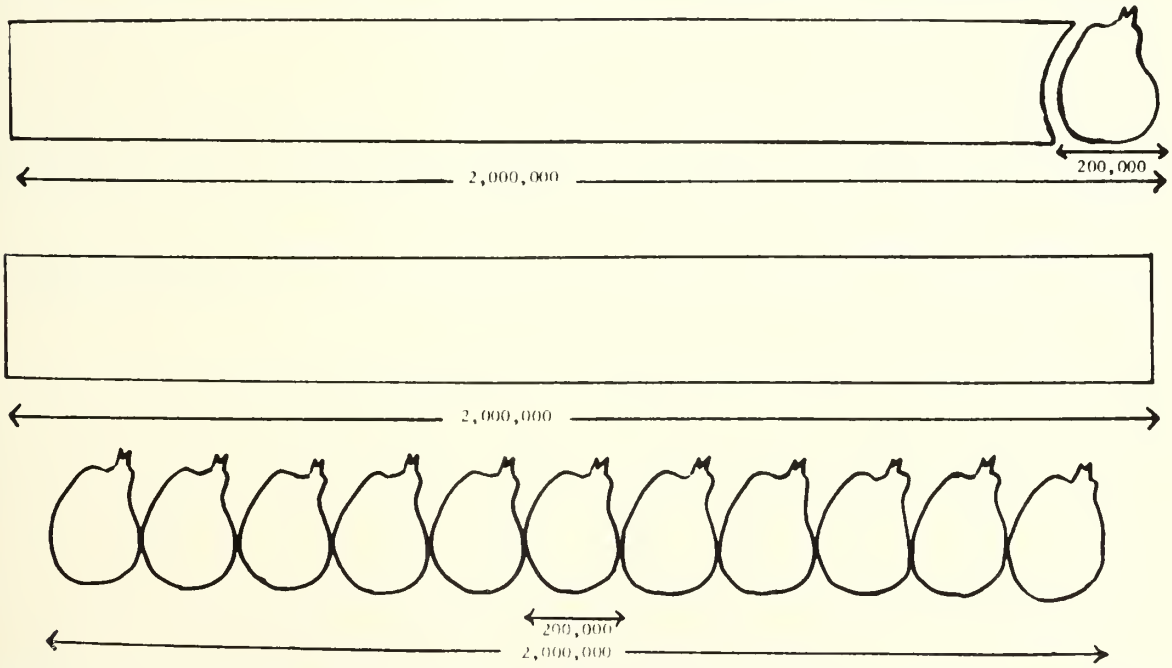

Figure 3.—Two current hypotheses for the structure of the Factor VIII molecule: upper drawing, a single molecule combining low molecular weight clotting sub-unit and high molecular weight antigen unit; lower drawing, two separate molecules, one of which is a polymer of low molecular weight clotting monomers, not identifiable by antisera.

ful in carrier detection by the antigen:Factor VIII ratio method, a workshop in Cleveland on this problem will be held so that a number of investigators can simultaneously attempt to segregate the same set of coded carrier and control plasmas. Eventual elucidation of this issue may have double value in allowing both improved genetic counseling and a more precise concept of the Factor VIII molecule.

The Molecular Hypotheses and the Inhibition Problem

My last concern this morning is the relationship between the molecular hypotheses and the inhibitor problem. At present we have no idea why a 5- to 10-percent fraction of hemophilic patients is susceptible to antibody formation while 90 percent can be transfused with impunity. It is conceivable that each hemophilic family possesses in the Factor VIII molecule a slightly different mutation in the region of the active site and that although many of these mutations result in essentially total loss of clotting activity, only some of them are sufficiently drastic to allow normal Factor VIII to be immunogenic in those recipients. We could reconcile such a concept with either version of the structure we have been considering.

A perhaps simpler, but equally difficult hypothesis to investigate, would be that the range of Factor VIII levels observed in both normal and hemophilic persons is produced by a regulatory gene rather than a structural one. It may be that 90 percent of severe hemophilic patients have an altered regulatory gene which permits a trace amount of Factor VIII synthesis but that the 10 percent who develop inhibitors have a regulatory gene which permits none whatsoever. Patients totally lacking those antigenic determinants would, not surprisingly, be likely to respond to Factor VIII infusions as to foreign proteins. However, we would expect such a large molecule to provoke a number of antibodies with different specificities and therefore to be immunoprecipitable. It is possible that our failure to observe precipitation is owing to the fact that the quantity of Factor VIII in normal plasma, or even concentrates, is too small for detection by this technique. We know, in fact, that this quantity is less than 50 micrograms per liter, but we do not know how much less.

This might be an appropriate point at which to brag about the sensitivity of clotting assays. When Leon Hayer at the University of Connecticut labeled the human antibody with ^{125}I and then reacted it with concentrated Factor VIII, he could detect no binding of label even though antibody obviously had been bound because the Factor VIII was completely inhibited. On the other hand, when we measure Factor VIII in a clotting assay, we have to dilute the plasma sample 1 part to 100 in order to avoid saturation of the clotting system with Factor VIII.

For the present, then, we have no corresponding sensitive detection technique for nonclotting Factor VIII, if such a thing exists, and this is where the frontier lies for cracking the inhibitor problem and, probably, the carrier problem as well. I think a realistic appraisal is that the easy problems have been solved in this field. The remaining ones are tough. I wish we had Paul Aggeler here to help.

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Important Advances in Clinical Medicine

Epitomes of Progress—Psychiatry

The Scientific Board of the California Medical Association presents the following inventory of items of progress in Psychiatry. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in Psychiatry which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Psychiatry of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, California Medical Association, 731 Market St., San Francisco, CA 94103

Sleepwalking

A REVIEW of the recent literature and several dozen cases of adult somnambulism indicates the following, some of which represent changes from earlier-held views:

- There appears to be no direct association between sleepwalking and dreaming, since the former occurs exclusively during stage IV sleep, that without rapid eye movement (REM). This of course does not question the views of those who attach genetic and dynamic importance to somnambulistic behavior, but merely removes it from the specific category of dream phenomena.
- There appears to be diminishing evidence to link sleepwalking with serious or disabling emotional disturbance. Although there is room for controversy in this area, several studies have indicated normal or near-normal distributions with respect to intelligence, education, social functioning and so forth.
- Consistent with the above, there is increasing evidence that, although pediatric cases appear much more common, somnambulistic behavior can also be easily found in segments (at least) of the young adult population.
- Strong evidence now exists that many if not most sleepwalkers show a possibly causal electroencephalographic "immaturity," an electrical finding which does not seem to correlate with any overt functional or organic abnormality when the person is awake.
- There is little evidence to support the once widely-held association of primary somnambulism with convulsive disorder.
- Past findings of some association of somnambulism with past traumata, enuresis and some other nighttime behaviors, and family histories of sleepwalking are, in general, replicated. Also apparently established is the preponderance of males versus females with the symptom and the finding that children who exhibit somnambulism usually

do not carry it into adult life, either as sleepwalking behavior or as a disabling form of functional disorder.

The various treatments for sleepwalking have covered a wide range of endeavor over the years, including somatic, pharmacologic and psychotherapeutic modalities. The author knows of no studies which show significant numbers of cures in adults, although there are a few anecdotal reports in the literature. One approach which may be promising involves hypnosis and the teaching of arousal cues. Benzodiazepine-based sleeping medications have been suggested because of their ability to specifically decrease stage IV sleep time. In addition, the author has suggested that, because of some of the dynamic and organic similarities to enuresis, tricyclic antidepressants might be studied on an empirical basis. To the author's knowledge, neither of these families of drugs has been explored in this context.

WILLIAM H. REID, MD

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Technique of Rapid Tranquilization

METHODS TO SAFELY and effectively tranquilize violent, agitated and psychotic patients have recently been proposed in the psychiatric literature. Uncontrolled severe psychomotor agitation and assaultiveness associated with various psychopathological states can result in injury to the patient and others, physical debilitation and exhaustion (life threatening, in some cases of mania and catatonic excitement), and needless prolongation of time spent in hospital. Benefits of providing rapid and safe control of these target symptoms include shorter duration of overt psychosis, briefer hospital stay, lower treatment costs, conservation of nursing care time, less disruption of ward therapeutic milieu, less dependency and regression, and earlier receptiveness to psychotherapy.

Chlorpromazine and haloperidol are frequently selected medications for use in rapid tranquilization; both are potent and proven antipsychotic agents, are safe when appropriately managed and can be dispensed orally and parenterally. The phenothiazine chlorpromazine tends to cause hypotension in susceptible persons, a disadvantage; its sedative effect may be desirable when physical agitation is severe. Haloperidol, a butyrophenone, is less sedating, sometimes an advantage when fear and suspiciousness are factors. Its use, however, is associated with a higher incidence of dystonic reactions than chlorpromazine.

One method suggests simply administering 50 mg of chlorpromazine intramuscularly or 5 mg of haloperidol intramuscularly at 30 minute intervals until adequate control of target symptoms is achieved, followed by establishing an oral maintenance dose. A somewhat more refined method requires that a test dose of 50 mg of chlorpromazine or 5 mg of haloperidol be administered orally after checking vital signs. (Vital signs, especially blood pressure, should be monitored before each dose is given; if systolic pressure is below 90, the dose should be withheld. Hypotension is controlled by supportive measures and withholding medication. Acute dystonia is easily and rapidly relieved with benztropine mesylate [Cogentin®], 1 or 2 mg given intramuscularly.) Doses are adjusted depending on response to the test dose, chlorpromazine being used at 50 to 200 mg given orally each hour and haloperidol at 5 to 10 mg given orally each hour (usually about half the oral dose if given parenterally). Adequate control of symptoms is usually obtained within six to eight hours.

After the desired control of symptoms is achieved, the daily maintenance dose is determined by prescribing two thirds of the twenty-four hour rate in divided doses. For example, if 600 mg of chlorpromazine are required over six hours for control of symptoms, then the 24-hour rate is 2,400 mg; two thirds of this amount in divided dosage would be 400 mg four times daily.

The patient should be allowed to sleep (adequate tranquilization being assumed if patient is asleep), keeping in mind that many psychotic patients come to the hospital following a period of sleep disturbance. Drowsiness associated with antipsychotic drugs predictably diminishes on the third day of use. Psychotherapy can usually be implemented at that time.

NOEL L. HOELL, MD

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The "Jet Lag" Syndrome

"JET LAG" OR "TRAVELERS BLUES" is the result of transmeridian flight. Rapidly crossing several time zones results in internal biorhythms being in conflict with external cues and leads to a desynchronosis syndrome. The major signs and symptoms of desynchronosis are, in order of decreasing frequency:

- Fatigue and psychomotor degradation;
- Insomnia, sleep/wake disturbances;
- Anxiety or depression;
- Gastrointestinal dysfunction and
- Other psychophysiological complaints.

The intensity of these signs and symptoms is a function of many factors including the age and experience of the traveler, the total time shift, the number of stopovers and—to some extent—the direction of travel within the United States. West to east travel tends to be more desynchronizing because of departure and arrival times.

In studying various circadian rhythms, we note both external desynchronosis (inside time versus outside time) and internal desynchronosis (with two rhythms being out of synchronosis with each other) associated with temporal translocations of three hours or more.

While the somatic changes may be annoying they are less critical than the performance and psychological changes. There may appear significant decrements in complex and fine perceptual-motor behaviors. The individual person can be expected to have some increase in errors in these behaviors and these errors in some professions and occupations may be clinically or professionally relevant—as with professional musicians, race drivers or surgeons.

The second consistent change has to do with altered moods. In recent work we note significant increases in depression, hostility and aggression. The nature of one's task may be such that increased moodiness, irritability and tendencies to express anger are of no relevance. Again, however, some occupations and professions can ill afford any such impairment in behavior—for instance, those involved with contract negotiations or diplomacy.

Awareness of these changes allows for prevention or reduction of untoward effects. Certain suggestions for the traveler may help to reduce jet lag symptoms:

- For short stays it is best to stay on "home" time;
- When traveling west to east go to bed progressively earlier before the trip (vice versa east to west);
- For important meetings leave several days earlier (our findings indicate that 48 hours are needed for resynchronosis);
- Arrange important activities at *your* normal peak times—meet your European colleagues in late afternoon or evening;
- Use food and alcohol sparingly during the flight and the first three days after arrival—alcohol (and most tranquilizers and hypnotics) interferes with rapid eye movement (REM) sleep;
- On long transmeridian flights arrange a halfway stopover;
- Arrange your schedule to shorten the day rather than the night;
- Rest and relax for two days before working.

DONALD A. ROCKWELL, MD

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Suicide in Physicians

PHYSICIANS WHO KILL THEMSELVES present particular personal and professional tragedies. From 150 to 200 physicians annually are lost to this preventable problem. The pain and stigma are immense.

The following factors are among those responsible for physician suicide.

Selection: Persons with an obsessive-compulsive style of life are often selected by medical schools. Despite the productive advantages of such a style of life, it does carry with it a proneness to depression in midlife and an attendant risk of suicide.

Training: During training, encouragement to deny feelings and symptoms in students—for seemingly sound traditional reasons but with tragic outcomes—occurs. In addition, patients encourage a growing sense of omnipotence in students during training. Both of these factors result subsequently in a denial of physical and psychic pain

in physicians and reluctance to seek help for personal pain.

Professional Life: The demands of patient care —with its immense responsibility and grinding endless work with frequent failure—may lead to emotional bankruptcy, depression and ultimately to suicide if alternative rewards are not fostered.

What are the danger periods? These are unusual in physicians, in that the highest risk period is the peak of professional life—age 35 to 54 years. Secondary risk periods are similar to those in the general population: following the loss of a spouse to death or divorce, during training years, and anticipating or following retirement.

Ambitious, driven physicians who over-extend themselves and suffer from chronic pain are at risk. Such people tend to drink too much or misuse drugs or have troubled marriages.

One should be aware of losses that colleagues are experiencing and look for depression in the year following a significant loss. Three to nine months after the loss is the period of highest risk. Any significant change in life style may signal a risk period. Subtle cues of depression and pseudohumorous comments made about death and suicide should be taken seriously. Relatively gentle probing may elicit suicidal ideation in a physician who is ambivalent about suicide. A denial of one's own pain or that of a colleague is life endangering. Signs and symptoms of alcohol or drug abuse need confronting immediately since delay benefits no one.

Treatment

The major problem in treatment is the hesitancy in recognizing the problem. As a group, physicians are great deniers of problems in themselves and, by extension, in colleagues. A secondary problem is that as a group, physicians are poorly educated about suicide generally and hence less able to deal rationally with the risk. The secondary problem is slowly resolving as physicians began to recognize that depression and drug problems are quite treatable and, in physicians particularly, have a good prognosis. The problem of denial is more difficult. It requires a colleague who sees the danger signals to intervene. There is no alternative but to take the risk of angry rejection. Someone must do this. In some medical societies the past presidents individually or as a committee have served to help troubled physicians on referral from other members of the society and with psychiatric consultation. This may be a workable alternative that meets the needs of all. Opening a person-to-person channel of communication with the suicidal physician is literally the lifeline of treatment. Definitive treatment of the underlying depression, drug problem, marital problem, or the like, cannot take place until someone reaches out. To not take the risk of reaching out means risking another's life.

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EDITORIAL

Slow Virus Diseases

THE REVIEW BY DR. ADAMS elsewhere in this issue on the subject of persistent or slow virus diseases deals with a very broad subject of great current importance, particularly in regard to today's most significant health problems such as many of the chronic diseases including cancer, mental disabilities and even the process of aging itself.

A few points made by Dr. Adams—or ones that are derivative from his paper—will be highlighted and are selected solely on the basis of the prejudices of the writer of this editorial.

Dr. Adams appropriately emphasizes the critical role that the careful study of animal models such as scrapie of sheep, lymphocytic choriomeningitis of mice and malignancies of fowl has played in the development of our understanding of these diseases. However, it should be recognized that the tremendous progress in our understanding of the molecular biology of cell-virus interactions and genetics, much of which has evolved from the seminal studies with bacteriophage, has opened up new ways of thinking about virus diseases and provided a framework for constructing testable hypotheses that have been of particular value in cancer but are potentially more widely applicable to many of the chronic diseases. For example, the recognition that the genome of the bacteriophage could persist in infected bacteria and their progeny, only forming complete virus when provoked by various stimuli (Lysogeny), has been found to have possible counterparts in animals and man such as recurrent herpes simplex, herpes zoster, subacute sclerosing panencephalitis and the like. However, the discovery that virus infection could result in new inherited attributes of the host cell has had a profound influence upon the approach of investigators to the study of mammalian viruses that so far has proved particularly fruitful in regard to cancer.

The long interval between initiation of infection and the appearance of disease that characterizes slow, persistent infections has important implications for human disease but presents a very difficult problem in diagnosis.

It must be emphasized that slow and persistent virus infections are associated with two classes of agents: the conventional viruses that meet the usual morphologic and biochemical criteria and the unconventional agents that lack many features usually exhibited by viruses (indeed, one wonders whether they truly qualify as viruses).

The diseases that the latter agents are known to cause are scrapie of sheep, mink encephalopathy, and Kuru and Creutzfeldt-Jakob disease in man. They are all characterized by very long incubation periods, a slow but relentless course and symptoms and pathologic findings limited to the central nervous system—the latter characterized by neuron loss and vacuolization but with no evidence of inflammation. No antibodies against these agents have been noted nor has anything resembling a virion or specific structure been identified. They are unusually resistant to physical agents and nucleases. All in all, they present a fascinating and difficult problem, not too different from that once presented by conventional viruses when all that was known about them was that they replicated, caused disease and passed through filters that retained bacteria. The one outstanding difference that will make the unconventional viruses more difficult to study is the lack of antibodies to them. Thus, it is not possible to separate strains or detect their presence without animal inoculation. New ideas and approaches will be needed if we are to understand these curious agents and delineate their true importance in nature.

Recently a group of agents called viroids that cause diseases of plants has been described.[1] Viroids have some attributes in common with the

unconventional slow viruses in that they appear to lack any structural protein but consist only of naked ribonucleic acid (RNA). Studies of these agents may prove useful to our understanding of their animal counterparts.

An interesting and important matter to recognize is the extraordinary differences that are seen in the diseases produced by a single virus. Who would have anticipated that such an ordinary run-of-the-mill virus such as measles would be found to cause not only the acute illness of classical measles but a highly fatal indolent encephalitis (SSPE) from 1 to 20 or more years after the acute infection and to be a prime suspect as an etiologic agent of a chronic relapsing central nervous system disease—multiple sclerosis?

It is quite apparent that the simplistic view of a virus disease or infection as an acute self-limiting episode followed by immunity and elimination of the virus can no longer be sustained. It seems probable that persistence of virus in some form in some cells of the body is the more usual outcome, dependent to a considerable degree upon the age of the host at the time of infection and other factors relating to the immunologic capacity of the host and genetic characteristics of the virus. Persistent infection may be harmless or may cause disease by a variety of mechanisms. These include slowly progressive cell destruction and immune disease as the result of deposition of antibody-virus complexes or in response to cells antigenically altered by virus or by the activation of latent virus by a variety of mechanisms—which include alteration of immune responsiveness due to disease, aging or immunosuppressive therapy.

Speculation concerning the role of viruses in a variety of disease states can easily sound like science fiction. However, on the basis of what we now know of viral replication and the intimate relationship between viral nucleic acids and the genetic apparatus of the cell, extraordinary possibilities become hypothetically feasible. Therefore, it would seem most likely that it is only a matter of time until at least some human cancers are proven to be caused by viruses. An etiologic role of viruses, particularly measles, in multiple sclerosis is highly probable. Animal models exist that implicate viruses in conditions that resemble multiple myeloma and various of the so-called autoimmune diseases and, as already pointed out, theoretical grounds also exist to support such an hypothesis. Gajdusek[2] has stated that the pathology of the spongioform encephalopathies may resemble the process of normal aging and has raised the question as to whether or not viruses may accelerate the rate of aging.

Far out ideas? Perhaps, and certainly not easy to prove, but with viruses it is hard to conceive of anything as completely impossible. However, keep in mind that it is a virologist speaking.

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The Fluoridation of Drinking Water

THE FLUORIDATION of drinking water continues to be a public health issue in many places in the United States. It has been and remains the subject of scientific, social, economic and political scrutiny by both its advocates and its opponents. The subject is examined further elsewhere in this issue of THE WESTERN JOURNAL OF MEDICINE, this time in relationship to dietary fluoride ingestion.

It is perhaps worth noting that as recently as last December the House of Delegates of the American Medical Association adopted upon recommendation of its Council on Foods and Nutrition[1] a statement on fluoridation which includes the following significant comment:

"No alternative techniques for the prophylactic application of fluorides can at present replace the fluoridation of drinking water as an effective and practical public health measure. Where water fluoridation at optimal levels cannot be used, however, other ways of supplying the proper amount of fluoride should be encouraged."

Until there is convincing evidence to the contrary we believe the fluoridation of drinking water is a desirable public health measure and that it should continue to be supported by the medical profession.

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The Hemophilioid Diseases and Factor VIII

Clinical Molecular Biology

In this current issue Dr. Judith Pool has described the current unsatisfactory state of affairs regarding Factor VIII and Hemophilia A. Few areas of disease due to hereditable molecular defects have aroused as much inquiry and consternation as that concerned with abnormalities of Factor VIII—antihemophiliac factor, for the problems are of major import in the care of patients and management of national blood resources. Contrary to anticipation, the hereditable and acquired hemorrhagic diseases associated with decreased Factor VIII procoagulant activity present not as a clinically homogeneous set of patients but as two generic disease sets. This seemingly uncomfortable observation has suggested a degree of complexity of the Factor VIII system consistent with results of recent studies that have attempted to unravel the molecular biology of Factor VIII and the diseases associated with defects of this molecular system.

Both classic Hemophilia A and von Willebrand's disease are associated with defects of the Factor VIII system, although the former is transmitted as a sex-linked recessive trait and the latter as an autosomal dominant trait—a circumstance that seems inconsistent with a common molecular defect. In patients with Hemophilia A, there is a deficiency in procoagulant capacity leading to deficient hemostasis which is most commonly manifest clinically as hemarthroses and excessive bleeding following traumatic events. Diagnostically, a normal bleeding time and normal platelet adhesiveness are noted in such patients, but there is a deficiency in plasma Factor VIII procoagulant activity. Although it was first thought that this procoagulant factor might not be synthesized in such patients, results of subsequent studies have established the presence in plasma of such patients of a molecule antigenically related to the Factor VIII system;[1] and Hemophilia A is currently thought to result from the synthesis of a defective Factor VIII procoagulant molecule.

In contrast, von Willebrand's disease is usually a rather mild hemorrhagic disease associated with easy bruising, a prolonged bleeding time and deficient platelet adhesiveness.[2] These very apparent hallmarks of defective platelet function are compounded by the usual association of reduced concentrations of Factor VIII procoagulant activity.

Can two clinically different diseases, with different modes of inheritance and different physiological dysfunctions, result from a common molecular defect? Such seems to be tenable only in the context of a more complex concept of the Factor VIII system. It has been suggested that Factor VIII is not a single uniform molecular entity regulated by a single genetic locus but represents a complex molecular system embodying at least two physiological activities, an antigenically identifiable molecule, two types of defects and the possible existence of more than one structural protein.[3-6] Although the investigation of the Factor VIII system has led to a number of proposed molecular concepts, the clinical diseases associated with inherited and acquired dysfunction of the Factor VIII system have become more objectively definable and rendered susceptible to objective clinical diagnosis.[1,2,5,6]

Factor VIII appears to be a heterogeneous molecular system exhibiting two identifiable physiological expressions and evidence of molecular heterogeneity.[7,8] Components of the system, apparently rather independent ones at that, are responsible on one hand for classical Factor VIII procoagulant activity (VIIIc) and on the other for imparting normal adhesiveness to platelets. This latter activity, referred to as von Willebrand factor (vWf)[4,9] is deficient in von Willebrand's disease and appears to be responsible for the increased bleeding time and many of the hemorrhagic manifestations characteristic of this disease.[2] Immunological analysis using heterologous antiserum to a high molecular weight component of the Factor VIII system have identified a molecule quantitatively deficient in von Willebrand's disease (vW Ag) but also directly correlated with VIIIc activity.[1] Although this represents a Factor VIII protein, human antibodies to VIIIc do not significantly bind this protein.[3] For this reason, we and others have referred to this as vW Ag rather than Factor VIII-like antigen. Current techniques permit measurement of these three entities within the Factor VIII system; however, attempts to establish an intrinsic relationship between these entities have not been successful,[3] and indeed it has been possible to physically dissociate VIIIc as a low molecular weight protein from vW Ag and vWf which are of high molecular weight.[4,7] Such studies have supported the concept that normal vW Ag may intrinsically possess vWf activity

but only serve as a carrier of VIIIc activity. Such a concept would satisfy the observed patterns of inheritance and immunological studies.

Using assays for these three Factor VIII entities (VIIIc, vW Ag, vWf), rather characteristic abnormalities have been observed in Hemophilia A and von Willebrand's disease—patterns that have resulted in more objective and reproducible clinical diagnosis of these diseases.[1,5] Whereas normal plasmas have an VIIIc/vW Ag ratio of approximately 1, Hemophilia A is characterized by normal concentrations of vW Ag but diminished VIIIc usually resulting in an VIIIc/vW Ag ratio of less than 0.1. The available Factor VIII system molecules provide little of the anticipated activity, suggesting that Hemophilia A results from synthesis of functionally defective molecules or molecules lacking the low molecular weight VIIIc component. Normal concentrations of vWf are present, usually providing a vWf/vW Ag ratio of unity, and the bleeding time and platelet adhesiveness are indeed normal. In contrast, a proportional decrease of all three components of the system are observed in typical von Willebrand's disease, suggesting that this usually results from decreased synthesis of the vW Ag molecule which may possess vWf and carry VIIIc. The molecular biology of von Willebrand's disease appears to be variable within certain limits and indeed disproportionate as well as proportionate decreases in each of the three components of the Factor VIII system have been described.[10]

Healthy heterozygous carriers of the Hemophilia A gene have mildly reduced VIIIc/vW Ag ratios, an observation that has led to attempts at carrier identification[11] as a more effective approach to preventive medicine through genetic counseling. Initial results of a recent workshop sponsored by the National Institutes of Health and the National Hemophilia Foundation have suggested that 80 to 85 percent of such carriers can be identified by this means of laboratory analysis. This represents an encouraging though not entirely acceptable level of confidence in carrier identification.

Results of transfusion studies have further supported the concept that the Factor VIII system may represent a complex set of proteins or a polymeric set of proteins exhibiting individual variation in structure and function. Strict proportionality of VIIIc, vW Ag and vWf is not always observed following transfusion of Factor VIII concentrates.[12,13] When patients with severe von Willebrand's disease are transfused with normal Factor VIII concentrates, the vW Ag level and vWf activity reach the anticipated levels; however, the VIIIc activity of their plasma increases well beyond the predicted level and is well in excess of the VIIIc/vW Ag ratio of approximately 1. Transfusion of the Factor VIII equivalent fraction, rich in vW Ag but lacking VIIIc, from Hemophilia A plasma induces an equivalent response including the appearance of increased VIIIc in the recipient. Such observations have led to the concept that transfusion of certain components of the Factor VIII system can stimulate synthesis of the procoagulant activity by the host, an observation well in keeping with the concept that the vW Ag molecule may be a carrier of the VIIIc component.

Regardless of the final resolution, elucidation of the molecular biology of Factor VIII will undoubtedly provide a basis for understanding the pathogenesis of the associated hemophilioid diseases, and it is to be hoped that investigative activities will permit more effective carrier detection. Finally, it is anticipated that more efficient preparation and judicious therapeutic use of Factor VIII proteins will facilitate the most efficient clinical management of Hemophilia A and von Willebrand's disease within the limits of available blood resources.

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An Editorial Essay

The "Malpractice" Crisis

THE CURRENT "malpractice" crisis, though predictable, was unexpected in terms of suddenness and scope. It is an immediate crisis in some parts of the country and is likely to become a national crisis perhaps before the year is out. The pocketbooks of physicians, patients, attorneys and the public are all directly involved—as well as the availability of patient care. As might be expected, there are many uninformed opinions being loudly expressed and there is considerable emotional outcry.

The sudden inability of physicians to get professional liability insurance coverage at a price their small business (someone has called it a "mom and pop store" kind of operation) can afford is what precipitated the crisis. Many physicians have suddenly found themselves with hard choices. Should they continue to practice without insurance, stop practice entirely or take a walk until things settle down? If they are young, should they (indeed, can they) start their own practice at all? In most cases none of these choices really makes sense. The first places not only the physician but his family in serious and unjustifiable financial jeopardy. Most do not want, are not ready or cannot afford to retire. To take a walk means either to carry the overhead for their assistants and office indefinitely or lose them. Physicians about to enter practice are often already heavily in debt and to incur a debt of many more thousands of dollars before they see their first patient may not seem to them to make sense. It is worth emphasizing that what is at issue here is not only the cost but the availability of physicians for patient care.

There are many who have ready and often simplistic solutions for this crisis. Unfortunately the problem is immensely complex and neither the diagnosis nor the remedy is proving to be simple or easy. The following are some of the factors which appear to bear upon the solution.

- *The insurance carriers* find themselves with diminishing resources due to the recession (specifically, a troubled stock market), and with mounting costs because of the increasing number of incidents undergoing litigation and the escalating size of the awards. Under the present laws and the present application of them, they see no adequate controls on their future losses and no adequate way to predict them. And, they have a responsibility to their stockholders to run their business prudently and without undue losses.
- *The attorneys* appear to get their fees in all cases except those taken on a contingency basis where the case is not won. Attorneys' fees are awarded often at considerable expense to the amount adjudged to the injured patient. Attorneys are improving their skills at trial strategy and tactics, and are taking increasing advantage of the fact that mistakes in judgment or accidents in patient care do happen and of the fact that unfavorable outcomes may occur as one of the risks of whatever the treatment given. Legal doctrines such as res ipsa loquitur and the new latitude in who qualifies as an expert have enormously strengthened their hand.
- *The physicians* who have malpractice suits decided against them may be good or bad physicians. Most are not bad physicians—often quite the reverse, as it is the good physician who most often undertakes the more critical procedures in order to benefit his patients. To a considerable extent the risk is specialty related and reflects the types of patients a physician sees in his practice. The more serious the situation the greater is apt to be the malpractice risk for the physician. Physicians do not and can not pay the costs of malpractice judgments against them. They pass these costs on to their patients and the public.
- *Social forces* contribute importantly to this problem. Many people no longer expect to bear their own burdens, they expect society to share them. A corollary of this is that those who bear a burden through no fault of their own should be compensated by society. Also, this is an age of consumerism. These social forces affect the laws which are passed and the doctrines and judgments established by the courts. And in addition this has become a litigious society.
- *Economic factors* are also important. The rise in the frequency and amounts of the awards is seriously and adversely affecting the cost of medical care. The rising cost of malpractice insurance will influence the numbers of physicians who will be in practice and the kinds of practice they will be in. And then there are, and will be, the costs of defensive medicine practiced by those who remain in direct patient care.
- *Political considerations* become important

now that the malpractice issue has entered the political arena. The medical profession has sought help and relief from government. The government will therefore be part of the solution. It will be necessary to enact just laws—laws with justice for the injured patient, for the physician who is trying to do his best for his patient, for the public interest in good but not unnecessarily expensive medical care and, yes, for the attorneys who as advocates for the plaintiff patients and defendant physicians must represent their clients in the courts of law. It is to be hoped that whatever is done will not curtail the freedom of a practicing physician to do what he believes is best for his patient in any given situation.

- *The public* is obviously concerned, confused and somewhat worried. Forces beyond anyone's control seem to be at work. Their doctors, upon whom they have come to depend, may no longer be able or willing to take care of them. And if they can and do, their patients and the public must become aware that the costs will be higher and that these higher costs will be passed on to them.

By anyone's definition a crisis clearly exists. The present system is simply not working. Both the cost and the availability of medical care to the public is at stake. The American way of doing things is under great stress. There is urgent need for both immediate and long-term solutions. It is suggested that for both the aims should be to:

(1) Keep physicians in practice with professional liability insurance at a price they can afford to pay.

(2) Provide for a fair means of compensating the unfortunate victims of medical accidents without placing an undue financial burden upon other patients or the public.

(3) Recognize professional liability, including the costs of malpractice litigation, as a cost of medical care and one that should be controlled as much as any of the other escalating costs of health care.

(4) Avoid developing adversary attitudes. Adversary attitudes between doctors and their patients, between doctors and the government, or between the medical and legal professions serve no useful purpose. Adversary attitudes accomplish little in the solution of complex problems of human interdependence anyway, and in this situation they will only add to the costs and reduce both the efficacy, efficiency and quality of patient care.

—MSMW

CASE REPORTS

Refer to: Randazzo GP, Ford EA, Glauser FL: Methemoglobinemia caused by acute overdosage of phenazopyridine. West J Med 122:427-429, May 1975

Methemoglobinemia Caused by Acute Overdosage of Phenazopyridine

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SELF-INDUCED DRUG OVERDOSAGE is a commonly encountered clinical entity accounting for 10 percent of admissions in selected hospitals.[1] The signs and symptoms generally associated with such excessive usage of drugs varies from mild lethargy to loss of consciousness, respiratory failure and cyanosis. Uncommonly a patient will present with a history of excessive drug intake, altered level of consciousness and cyanosis, in which the bluish discoloration stems not from the severe hypoxemia associated with respiratory depression but from a toxic methemoglobinemia induced from the drug ingested. In this brief report we present such a case secondary to self-induced overdose of a medication containing phenazopyridine.

Report of a Case

A 43-year-old white man was admitted to Orange County Medical Center on February 13, 1974 with a history of confusion for less than 12 hours. The patient had been admitted once before, six months earlier, for intentional overdose of diazepam and meprobamate, and had recovered without complications.

Since the first admission to hospital, the patient had remained depressed and had sharply increased his intake of alcohol. On the day of admission he had been drinking heavily. His wife reported that he had taken approximately 50 tablets of a urinary anesthetic containing 150 mg of phenazopyridine, 0.3 mg of hyoscyamine hydrobromide and 15 mg of butabarbital per tablet (Dolonil®). The patient was admitted to the ward due to his confusional state and the possibility of impending respiratory failure. On physical examination, rectal temperature was 38.2°C (100.8°F), pulse rate was 130 beats per minute and regular and blood pressure 130/70 mm of mercury. Except for lethargy and a transient clonus of the left leg, no other abnormalities were noted.

Within two hours of admission, the patient was noted to be severely cyanotic and more lethargic but there were no changes in vital signs. Results of immediate laboratory studies showed a hemoglobin of 16.5 grams per 100 ml with a hematocrit of 49 percent and a leukocyte count of 19,500 with shift to the left. The urine was seen to have a bright orange coloration. Arterial oxygen partial pressure (PaO_2) was 87 and arterial carbon dioxide partial pressure ($PaCO_2$) was 37 mm of mercury; pH was 7.46 (inspired concentration of oxygen [F_IO_2] was 0.21). A hypnotic screen showed blood short acting barbiturate level at 1 mg per 100 ml and long acting barbiturate level of 0.4 mg per 100 ml. Serum methemoglobin level was 6.4 grams per 100 ml giving a percent hemoglobin saturation of 43.8 percent.

After initial treatment with 90 mg of methylene blue administered intravenously, the patient's confusion lessened somewhat. Seven hours later his mental state had cleared nicely but the patient was still blue and a repeat determination of methemoglobin level was 3.5 grams per 100 ml and 23.7 percent saturation. Another 70 mg of methylene blue was administered and again there was rapid improvement. On the second hospital day the hematocrit had fallen to 38 percent (no reticulocyte count or Heinz body preparations were done).

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Submitted July 23, 1974.
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A test of blood glucose 6-phosphate dehydrogenase (6-PD) gave results at the lower limit of normal. The remainder of the hospital course was highlighted by rapid and complete recovery.

Discussion

Previously reported cases of methemoglobinemia resulting from phenazopyridine hydrochloride ingestion have described acute accidental overdose in infants.[2-4] Intoxication due to iatrogenic overdose in an infant[5] and subacute intoxication in adults[6] which resulted from the use of therapeutic doses in the face of renal compromise also have been reported. The patient described in this communication is the first reported case of acute adult overdose with phenazopyridine (Pyridium®).

Phenazopyridine is an azo dye which was originally used as a urinary antiseptic but most recently has seen general use as a urinary analgesic[7] or urinary chromagen to facilitate urologic procedures. A large number of aromatic compounds, theoretically capable of producing free radicals (chemical intermediates by virtue of their resonance properties) have been reported to produce clinical methemoglobinemia.[8] These redox agents are felt to act as intermediates between oxygen and hemoglobin in the reaction producing ferriheme.[9] Greenberg and Wong noted the similarity of the chemical structure of Pyridium with those of phenylhydrazine and acetylphenylhydrazine, both potent producers of methemoglobin and Heinz bodies in *in vitro* systems with suspended red blood cells.[6,9] The formulas of six organic agents commonly associated with methemoglobinemia are depicted in Figure 1 illustrating the structural similarities to phenazopyridine in this group of agents.

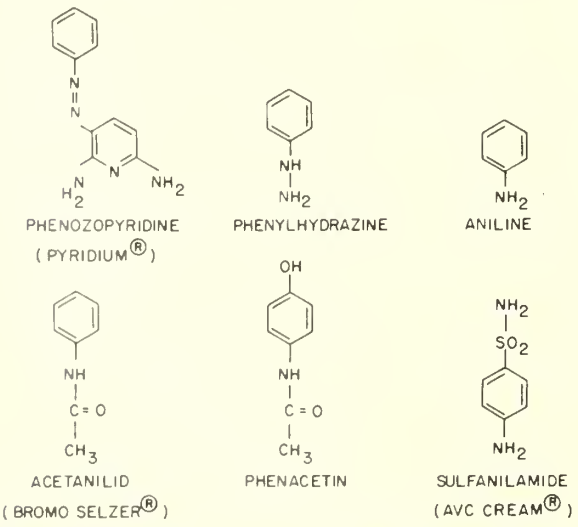

Figure 1.—Chemical structure of some common drugs associated with methemoglobinemia.

A large number of proprietary products containing phenazopyridine singly, in combination with an antibacterial or antibiotic agent, or with a parasympatholytic agent and barbiturate are available

TABLE 1

Agent and Components

1. Azo Gantanol® (Roche)
   sulfamethoxazole 500 mg
   phenazopyridine 100 mg
2. Azo Gantrisin® (Roche)
   sulfamethoxazole 500 mg
   phenazopyridine 50 mg
3. Azo-Mandelamine® (Warner/Chilcott)
   methenamine mandelate 500 mg
   phenazopyridine 50 mg
4. Azo-STAT® (Westerfield)
   phenazopyridine 200 mg
5. Dolonil® (Warner/Chilcott)
   phenazopyridine 150 mg
   hyoscyamine hydrobromide 0.3 mg
   butabarbital 15 mg
6. Donnasep® (Robins)
   methenamine mandelate 500 mg
   phenazopyridine 50 mg
   hyoscyamine sulfate 0.0519 mg
   atropine sulfate 0.0097 mg
   hyoscine hydrobromide 0.0033 mg
   phenobarbital 8.1 mg
7. Pyridium® (Warner/Chilcott)
   phenazopyridine 200 mg or 100 mg
8. SignaSul Azopak® (American Urologicals)
   phenazopyridine 200 mg
   sulfamethizole 1.0 mg
9. Suladyne® (Stuart)
   phenazopyridine 75 mg
   sulfadiazine 125 mg
   sulfamethizole 125 mg
10. Thiosulfil Duo-Pak® (Ayerst)
    phenazopyridine 75 mg
    sulfamethizole 0.5 gram
11. Thiosulfil-A® (Ayerst)
    sulfamethizole 0.5 gram
    phenazopyridine 50 mg
12. URI-PAK® (Westerfield)
    phenazopyridine 200 mg
    sulfamethizole 0.5 gram
13. Uri-Tet Azopak® (American Urologicals)
    oxytetracycline hydrochloride 250 mg
    phenazopyridine 200 mg
14. Azotrex® (Bristol)
    sulfamethizole 250 mg
    tetracycline phosphate 125 mg
    phenazopyridine 50 mg
15. Urobiotic®—250 (Pfizer)
    sulfamethizole 250 mg
    phenazopyridine 50 mg
    oxytetracycline hydrochloride 250 mg

to the physician for treatment of urinary tract infections. The product information inserts for many of these agents either do not list methemoglobinemia as an adverse reaction of their use or overdose, or ascribe such toxic potential only to the sulfonamide moiety of a combination. Table 1 lists the proprietary products now available for prescription which contain phenazopyridine hydrochloride.

Our patient presented as a typical overdose, that is, altered consciousness and a history of ingestion. Normally treatment would have consisted of passage of an endotracheal tube, gastric lavage, diuresis and respiratory management.[10] Fortunately, due to his level of consciousness, it was elected to observe the patient and only administer supportive care. Once the cyanosis became evident, an arterial PO_2 study showed normal oxygenation and the diagnosis of methemoglobinemia was entertained and, once diagnosed, treated appropriately. The peculiar orange color of the urine should probably have given us a clue much earlier that he may have ingested phenazopyridine as this drug is well known to cause this phenomenon.

This case points out the need for awareness of the peculiar toxicity of the phenazopyridine group of drugs. When these drugs are abused, altered consciousness and cyanosis may indicate methemoglobinemia and not respiratory failure.

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LETTERS *to the Editor*

From a Gout Sufferer

To the Editor: I have been a proven gout sufferer for approximately ten years. I have found the dietary substitution of lamb striated muscle (chops, roasts, etc.) for ALL cellular animal protein has resulted in the absence of gouty attacks and repeated blood uric acid levels have been normal in the last year.

I have also noted the new soy bean based meat substitutes have been a source of additional dietary protein without affecting my blood uric acid level.

Robert A. Sills, MD
Alhambra, California

Ophthalmology and Medical Ethics

To the Editor: At the Sunday, February 23, 1975 Specialty Section of the 104th Annual Session of the California Medical Association Meeting in Los Angeles, the subject of medical ethics and ophthalmology was discussed in detail. The discussion followed a request by several members that something tangible should be done to stop the unethical actions of some members in the various county medical societies. Specifically, members have been photographed holding prosthetic devices and standing next to medical apparatus, extensively and directly quoted in the lay press when they were not representatives of organized medicine, appeared on television without clearance by local medical societies, and other actions which could be interpreted to be advertising and solicitation of patients.

It could be stated by some that their actions were accomplished out of ignorance. With this possibility (however remote) the membership had enumerated for them numerous well established codes of ethics concerning our respective societies, state, sectional and national organizations. For example, the Los Angeles Society of Ophthalmology has within its agreement of membership that the member shall be "bound to the principles of Medical Ethics of the American Medical Association." The Los Angeles County Medical Association has rulings of the Committee on Ethics concerning press releases and endorsements which should be adhered to. The San Francisco, Riverside, and other societies have similar rulings. The State of California Board of Medical Examiners [Business and Professions Code] Paragraph 2380 concerns itself with advertising and what constitutes unprofessional conduct. The Pacific Coast Oto-Ophthalmological Society, Section 9 of its bylaws, states "the code of ethics of the American Medical Association was adopted and made part of the bylaws by the Society." The American Medical Association [*Principles of Medical Ethics*] section 5, #15 concerns itself with solicitation of patients, while #17 is concerned with the use of proper advertising media. Section 10 importantly covers the relationship of the physician to the media of public information and should be read and understood by all physicians. Number 4 under this section covers advertising in the daily press; #5 concerns medical public relations; #7 covers the release of medical information to the press; #13 relates to the relationship of the physician with communication media.

Advances in technology continue in ophthalmology. The CMA Ophthalmology Specialty Section in no way wishes to restrain individuals from advancing our specialty. It does wish to emphasize that there are ethical and unethical means by which information can be disseminated. A unanimous resolution was proposed and passed by those in attendance as follows: "The CMA Ophthalmology Specialty Section resolves and reaffirms that as Ophthalmologists we should abide by the Principles of Medical Ethics—Rules of the Judicial Council of the American Medical Association dated 1969, and to the rulings of our respective medical societies." I hope that you will print this in the Letters to the Editor, so that those who were not in attendance will be aware of our action, and report any violations to their respective medical societies.

Robert E. Christensen, MD
Chairman, CMA Ophthalmology Specialty Section 1974-1975
Los Angeles

Refer to: Lee JR: Optimal fluoridation—The concept and its application to municipal water fluoridation (A Public Health Issue). West J Med 122:431-436, May 1975

A PUBLIC HEALTH ISSUE

Optimal Fluoridation

The Concept and Its Application to Municipal Water Fluoridation

JOHN R. LEE, MD, *Mill Valley, California*

Optimal fluoridation has been defined as that fluoride exposure which confers maximal cariostasis with minimal toxicity and its values have been previously determined to be 0.5 to 1 mg per day for infants and 1 to 1.5 mg per day for an average child.

Total fluoride ingestion and urine excretion were studied in Marin County, California, children in 1973 before municipal water fluoridation. Results showed fluoride exposure to be higher than anticipated and fulfilled previously accepted criteria for optimal fluoridation. Present and future water fluoridation plans need to be reevaluated in light of total environmental fluoride exposure.

IN THE PAST THREE DECADES, the addition of fluoride ions to municipal water supplies has been strenuously promoted by many public health officials as a public health measure to reduce the incidence of dental caries. Often these measures have been just as strenuously resisted by persons whose objections stem from questions of presumed efficacy, fears of potential fluoride toxicity and the abridgment of personal rights. Despite the passage of 30 years, the fluoride controversy swirls up anew whenever a community undertakes to enforce acceptance of fluoridation of its water supply by the process of majority vote, itself a technique quite curious and unique among public health affairs.

The author is Chairman, Environmental Health Committee, Marin Medical Society.

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During 1973, Marin County, California, residents within the boundaries of the Marin Municipal Water District (MMWD) found themselves involved for the third time in this controversy. This time, however, a new question was raised, the question of optimal fluoridation or the precxisting sufficiency of dietary fluoride intake. This resulted in intensive investigation by the local medical society—particularly its committee on environmental health, plus other interested members. The purpose of this paper is to review the nature of the problem, to define optimal fluoridation, to present the available data pertaining to fluoride intake in "unfluoridated" Marin County when its water supply contained 0.1 parts per million (ppm) of fluoride and to discuss logical inferences and their potential application.

The history of fluoridation is interesting in that

its role in cariostasis devolved from research not into the problem of tooth decay but into the problem of mottled enamel. Before 1920, this conspicuous developmental hypoplastic staining of the teeth was found to be endemic in some areas of this and other countries. In 1916, a dentist, F. S. McKay of Colorado, reported this endemic phenomenon.[1] Later he became convinced this was probably associated with some unknown element in the water supply.[2] In 1931, the causative agent was identified simultaneously by two separate research groups as fluoride[3,4] and mottled enamel became known as dental fluorosis. Because of this discovery, the United States Public Health Service assigned a staff dentist, H. Trendley Dean, the task of determining the level of fluoride in water which would not cause this deleterious effect.[5] Dean was able to show that dental fluorosis became detectable when fluoride concentrations rose over 0.6 ppm and, at higher levels, the severity of mottling rose sharply until, at concentrations of 2 ppm or above, dental fluorosis became "an acute and urgent public health problem."[6] Concurrently, Dean, aware of McKay's observation that mottled teeth appeared to be relatively free of caries, gathered data which were published in 1938 and which confirmed this relationship.[7] Subsequently, Dean and other Public Health Service researchers surveyed naturally fluoridated communities in order to establish quantitatively the relationship between fluoride in drinking water and caries incidence.[5,6]

By 1942, Dean and his co-workers had concluded that maximal cariostasis occurred at a fluoride concentration of 1 ppm (1 mg per liter) at which level only 10 percent of the population was affected with the mildest degree of dental fluorosis.[6] Fluoride concentrations above 1 ppm did not confer significant additional cariostasis but did sharply increase the incidence of dental fluorosis. Consequently, in 1943 the Public Health Service established a drinking water standard of 1 ppm as the maximum allowable fluoride concentration.[8] (In 1962, a range of 0.7 to 1.2 ppm of fluoride was recommended depending inversely on temperature ranges.) During the 1940's extensive investigation established that, although fluoride is ubiquitous throughout nature, dietary intake of fluoride other than in water was essentially quite minimal.

McClure's classic summary in 1943 of daily intake of fluoride from food and drinking water sources based on estimates from existing fluoride content of specific foods, showed that in a community with drinking water containing fluoride at 1 ppm the average quantity of fluoride contained in food and water consumed by those 1 through 9 years old was 0.4 to 1.4 mg per day.[9] Of this total, only 0.03 to 0.45 mg per day were usually obtained from the dry food, the rest coming from water. These same figures appeared consistently in public health publications for the next three decades.[10-12] In all these publications, optimal fluoride intake for the appropriate age groups is calculated as 1 to 1.5 mg per day from all sources. This was reaffirmed by the Academy of Pediatrics' Committee of Nutrition in 1972.[13] In their report they state that "in the temperate zone, fluoridated community water supplies are increased in fluoride content to a level of 1.0 ppm, thus providing, on the average, a total fluoride ingestion of 1.5 mg per day." This, they state, provides the "optimum fluoride intake for the growing child," as even "an adverse effect on tooth structure may result at intake levels above 5 mg." Thus the level of optimal fluoride intake is consistently and rather firmly established.

Despite the emphasis on water, however, there is no doubt that food fluoride, except of bone meal, is essentially just as well absorbed and available as the fluoride in water.[14] Even "96 percent of the fluoride from a calcium fluoride solution was absorbed" as Hodge states. According to the World Health Organization,[15] fluoride absorption from beverages containing fluoride ions "is as complete from them as from plain water." Fluoride absorption is nearly the same whether the fluoride was supplied in milk or in water.[14,15]

Optimal fluoridation can be stated to be the average daily absorption of 1 to 1.5 mg of fluoride, regardless of source, by the age group 1 to 12. The question facing residents of Marin County, relative to this concept of optimal fluoridation, was brought into focus by the recent findings of increased dietary fluoride sources. These dietary sources occur as fluoride is incorporated into the food chain by canning, bottling or other prepreparation of food;[16,17] by industrial fluoride as an air pollutant being absorbed by broad-leaved plants such as lettuce and cabbage;[18] by fluoride-polluted forage for food animals,[19] and by numerous other direct and indirect ways which inevitably affect humans.

Marier and Rose, at Canada's National Research Council, calculated food fluoride, assuming

all food processed in water at 1 ppm, and found that by 1963 food-chain fluoride was approximately 3½ times that which was found by earlier investigators.[16] Spencer and co-workers analyzed diets in the Veterans' Hospital at Hines, Illinois, and found a daily intake range of fluoride from 3.6 to 5.4 mg per day.[21] Children's cereals such as Grape-Nuts® and Wheaties®, milled in fluoridated Minneapolis, have shown the rather high fluoride values of 6.2 ppm and 10.1 ppm respectively.[22] In 1971, the United States Army Institute of Dental Research published a study of diets obtained in a "market basket" type analysis of foods collected in 1967 and 1968 by several teenage boys from supermarkets in fluoridated Baltimore.[23] Analysis of the diets included not only the foods purchased, but milk and water used in food preparation, plus beverages consumed. They were found to provide an average of 2.1 to 2.4 mg of fluoride per day. Consumption of water, per se, was not separated out of the beverage group which included soft drinks, tea, coffee and milk.

Though not a problem in Marin County, airborne fluoride can represent appreciable fluoride exposure. A 1970 publication of the United States Department of Agriculture Research Service states "airborne fluorides have caused more worldwide damage to domestic animals than any other air pollutant. . . . Whenever domestic animals exhibited fluorosis, several cases of human fluorosis were reported. . . . Man is much more sensitive than domestic animals to F [fluoride] toxicity."[20]

It should be recalled that the United States Food and Drug Administration issued a policy statement, published in 1953, which held that "fluorine intake is the same whether the fluoridated water is added in a food factory or in the home kitchen." The statement concludes that there should be appraisal of "probable fluorine intake from all sources other than the water supply."[24]

Making the natural assumption that foods sold in supermarket chain stores are the same, whether the store is in fluoridated San Francisco, for example, or in unfluoridated Marin County, the question of average daily fluoride intake by Marin children became a significant issue.

The Marin County Medical Society Environmental Health Committee opted for a direct approach to find the answer. Through Parent-Teacher Association contacts and other interested parties, a drive was made to compile, as accurately as possible, records of the food, snacks and beverages consumed in a day by an average child in the county. Eventually, 153 such day-food lists were compiled. Due to budgetary limitations, only 17 (chosen by chance lot) could be offered for fluoride analysis.

The Marin Food Fluoride Study

Design of the Study

The procedure used in the study was to obtain *duplicate* sample daily diets from Marin County children in the age groups 4 through 6, 7 through 9, 10 through 12, and 13 through 15 years of age and to submit each day's diet for individual total fluoride determination.

Duplicate meals (including school lunches and snacks) were prepared in the quantities consumed. The mothers were cautioned to duplicate only the amount each child actually had eaten, and to discard amounts equal to what the child left on the plate. Each full day's diet was placed in a fresh individual plastic container and fluids other than water were combined in milk cartons or sent along within their original containers. When poultry was part of the day's meal, the edible portions only were included, the bones discarded, similarly for meat bones, and the peels of oranges.

The individual duplicate daily diets were refrigerated overnight and delivered the next morning to a laboratory for analysis. An independent laboratory was selected from a list of laboratories regularly employed on research projects by the California State Department of Health, the State Department of Agriculture and the University of California. Each diet was homogenized, dried and analyzed using current methods of the Association of Official Analytical Chemists (AOAC). Three to four aliquots of each individual diet obtained an accuracy of 2.7 percent. The final figure is an average of aliquots (Table 1, Total Fluoride).

By fortuitous coincidence, a group of essentially pro-fluoridation dentists and pediatricians proceeded with an independent study involving urine fluoride excretion in 17 well Marin children, age 12 to 16. A report of this study was presented in testimony by a Public Health Department official to a State Board of Health meeting in Sacrament (June 1973) and made available to the press. These data indicated an excretion of fluoride in urine in the concentration range of 0.2 to 0.7 ppm in the absence of any supplemental fluoride or water fluoridation (MMWD water fluoride is approximately 0.1 ppm or less). Later in testi-

mony before the county medical society, Public Health Department officials stated that a total of 72 specimens were analyzed and similar results found. The exact figures from this study are unavailable to the author, though the mean was given as 0.34 ppm.

Analysis of Data

Admittedly the data are derived from small sample numbers. This, in the case of the food study limitation, was determined solely by the limits of economic realities. A larger study must await a future larger financial commitment. However, the reader should be assured that the literature concerning fluoride abounds with landmark research which involves samples of even smaller numbers.[25] While the Marin study may be criticized because it was not as extensive as might be desired, it does represent the only such data existent for this area and this time set.

The rather wide range of food fluoride found—as well as the wide range of urine fluorides reported—attest to the recognized wide variability of children's diets from day to day. Conversely, the narrow range found in the San Filippo and Battistone report (representing market basket choices of four teenage boys) is quite unlikely and atypical of results from other dietary fluoride studies.[26]

Bias in reporting to favor the investigators is a recognized potential source of error in sampling techniques such as those used in the food study. However, this is minimized by the fact that mothers are unlikely to know which foods are high or low in fluoride. It is certainly no less accurate or less meaningful than "market basket" studies.

Finally, it must be noted that before our Marin data were collected, no reports of intake in an "unfluoridated" community in the United States had been published for approximately 20 years.

Reliability and accuracy of spot tests of urine fluoride concentrations are not universally accepted. However, the accuracy of the mean of 72 urine samples was strongly defended by Public

TABLE. 1—*Total Food-Borne Fluoride, 1973*

Child (family initial)	*Age*	*Body Weight kg.*	*Body Weight lbs.*	*Complete Day's Diet (wet weight, inc. bev.) (grams)*	*Total Fluoride (milligrams)*	*Average Fluoride (per age range) (milligrams)*
C ...	5	20.9	46	1,620.1[1]*	0.900	
				1,651.6[2]	0.845	0.942
L ...	6	20.4	45	1,392.6[3]	1.062	
				1,433.9[4]	0.961	
N ...	7	29.5	65	1,124.5[5]	1.010	
C ...	7	24.5	54	1.651.6[6]	0.350	
				1,561.2[7]	0.850	1.114
C ...	9	32.7	72	1,465.0[8]	1.155	
				2,177.8[9]	2.205	
L ...	10	34.0	75	870.5[10]	0.235	
				993.1[11]	0.405	
L ...	12	47.7	105	1,124.1[12]	0.871	0.911
				2,323.3[13]	1.655	
N ...	12	59.0	130	1,773.1[14]	1.390	
C ...	14	54.5	120	2,363.0[15]	2.100	
				1,524.4[16]	1.055	1.518
G ...	14	43.2	95	..[17]†	1.400	

*Individual diets are discussed in the summary following. With some children, diets for two different days were collected.
†Weight not recorded.

INDIVIDUAL DIETS (Summary of Details)

The dietary patterns of these families had certain similarities common to many families with growing children, with convenience foods a little less than one third of the food, canned beverages used for mixing rather than fresh preparations, commercial breads and cakes.

BREAKFASTS consisted of fruits and juices, breads, protein and cereals: Cream of Wheat®, Wheaties®, granola (3, 5, 6, 14, 17), Cheerios® (3, 4, 13); bacon, sausage or other pork (7, 8, 9, 15, 16); eggs universally; and occasional pancakes, pop-ups and similar novelties.

LUNCHES were typically sandwiches with liverwurst, jack cheese, frankfurters, cold roast beef, salami or peanut butter (6, 7, 8, 15, 16); fresh fruits, apples, oranges, bananas; small commercial cakes. Diets (13) and (16) included one cup of tea each; diet (1) had half a cup of tea. Diet (7) had a tuna salad sandwich. Diets (15) and (9) had 1½ oz (Gortons®) minced clams (with juice) mixed in an 8 oz serving of Campbell's® mushroom soup. (See discussion below.)

SUPPERS included poultry (3, 5, 13, 14), lamb chop (10, 12), hamburger, ground beef or commercial specialty beef (1, 4, 8, 16, 17); roast beef, stew (2, 11), pork in various forms (6, 7, 9, 15). Seafood was missing from the supper meals. Diet (15) had a cup of tea. Cooked vegetables, potatoes, salads, ice cream for some, cake and fruit filled out the supper meals.

BEVERAGES were generally milk and skim milk, fruit juices, some Coca Cola®, and fruit-ades, hot chocolate and an occasional single cup of tea as noted.

SNACKS included jelly beans, Saltines®, milk shakes, a mayonnaise and mustard sandwich, cookies, salami, grapefruit and other fruit and small cakes.

DISCUSSION: Other than the small amounts of tea, the tuna salad sandwich, and the divided can of minced clams, sources of excess fluoride would require detailed food analyses to pinpoint.

The close readings in diets (1) and (2) (same child) which had similar volumes of food by weight, a half cup of tea (diet 1), no tea in diet (2), indicate that *volume* rather than a portion of high fluoride is more significant in determining the fluoride quantity. This is further exemplified in diet (9), in which the 1½ oz (which is a very small amount) of minced clams is also accompanied by a 50 percent greater amount of food than diet (8) (same subject, and no seafood).

The same trend is visible in diets (15) and (16), in which the small amount of minced clams also finds itself in a diet 50 percent greater by weight than the diet having no seafood (but one cup of tea in each meal, thus not a factor).

Diets (12) and (13) show a doubling of food volume and total fluoride, with one cup of tea in the larger volume diet (13).

It is very likely that in coastal regions seafood plays a more prominent role in the general diet than in inland areas. Certainly in the face of busy school schedules and as an alternative to higher priced meats, the convenience of canned tuna, sardines, clams, and the like, would seem to be a reasonable trend of our modern society.

Health officials testifying before the county medical society committee.

Comparing urine fluoride excretion with fluoride ingestion in these age groups is not an unfamiliar procedure. The relationship is expressed in the mathematical formula $U = -0.13 + 0.53 A$ where U = mg of fluoride excreted in 24 hours and A = mg of fluoride absorbed in 24 hours in young people whose bone and teeth binding sites are not yet fluoride saturated.[27] The urine test results, being reported in fluoride *concentrations*, are translated into 24-hour *amounts* by assuming a 24-hour urine volume in the expected range of 1 to 1.4 liters for this age. Using this assumption and applying the function, urine fluoride excretions are found to indicate a daily absorbed fluoride level of 1 to 2.2 mg per day with the mean, derived from the 72 urine tests, being 1.4 mg per day.

These urine-derived measurements of fluoride intake are seen to correspond remarkably closely to the food fluoride study results. The relationship among fluoride measurements in McClure's 1943 fluoridated communities, Marin's 1973 "unfluoridated" community (as found in both the food and the urine excretion studies) and the 1967-1968 Baltimore market basket food study is shown in Chart 1.

Discussion

Clearly, both studies in Marin County before water fluoridation show that Marin children ingest and absorb a quantity of fluoride which is in

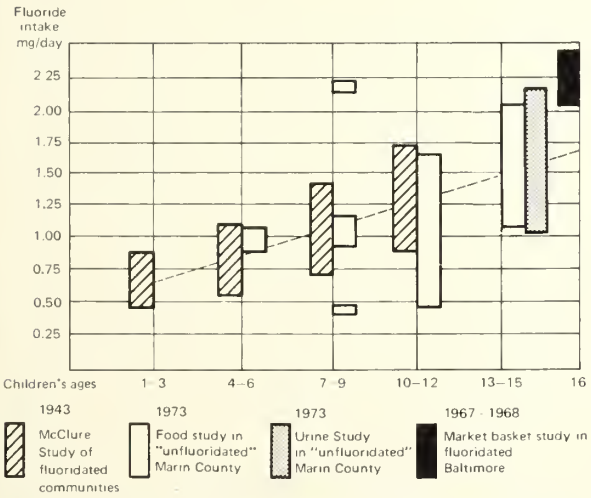

Chart 1.—Relationship of fluoride concentrations found in four studies. Broken line (---) indicates expected mean fluoride intake in an optimally fluoridated community.

the optimal range, as established and consistently enunciated by all responsible dental, pediatric and public health agencies for the past 30 years. Even without questioning the still disputed relative efficacy of fluoride in cariostasis or the philosophical argument of personal rights, it must surely be agreed that there exists no justification for exceeding optimal dosage. The acceptable range is relatively quite narrow as stated by the Committee of Nutrition of the American Academy of Pediatrics.[13] Yet it often seems to be forgotten, even by medical professionals, that fluoride is primarily a toxin.[28]

The question of whether it can, in extremely minute amounts, also be classified as a nutrient is a moot point since its ubiquity rules out any chance of an insufficient supply from that point of view.

The concept of optimal dosage, it must be reemphasized, states that beyond a given dosage no further benefits are conferred *and* toxic effects become more and more likely.

Presumably by stimulating increased water intake, warmer climates often lead to obvious endemic fluorosis, even when fluoride concentration is in respectable ranges. There is, for example, a recent report in *Lancet* by the National Institute of Nutrition, Indian Council of Medical Research, Hyderabad, India,[29] which showed endemic fluorosis in areas with fluoride levels of 3.5 ppm associated with kyphosis, exostoses, osteoporosis and a disabling genu valgum. It is of particular interest that levels of serum calcium, phosphorus and alkaline-phosphatase activity were normal.

Even in the cooler climate of Minnesota, increased water intake at conventional fluoride concentrations, under certain circumstances, has been found to be deleterious. A recent report from the Mayo Clinic[30] showed the development of osteofluorosis in two teenagers with preexisting renal disease, which obviously affected the intake and possibly the clearance of fluoride. Undoubtedly, there exist occupational and other circumstances which will greatly increase the fluid intake and thus the fluoride absorption when the available water supply is used as the carrying vehicle for fluoride.

Conclusion

Optimal fluoridation, by previously accepted standards, occurs when an average child in the formative age group receives 0.4 to 1.5 mg of fluoride per day. Seventeen sample diets of Marin

children were analyzed for total fluoride content. An average daily intake of 0.9 to 1.5 mg was found.

Urine fluoride excretion by Marin children had been reported and these results are analyzed. They are found to correspond very closely to results of a study of fluoride ingestion.

By these standards, the available data suggest that Marin County was an optimally fluoridated community without the addition of supplemental water fluoridation. The decision of the State Board of Health to raise the Marin County water fluoride level from 0.1 ppm to a maximum of 1.2 ppm is difficult to reconcile with these facts.

Recognizing the limitation of our small sampling, it is clear that further large-scale studies should be accomplished as soon as possible not only in Marin County but in other communities, both fluoridated and "unfluoridated."

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A PUBLIC HEALTH ISSUE

Editorial Comment

Water Fluoridation and Dietary Fluoride Ingestion

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THE FLUORIDATION of water supplies to an optimal *concentration* of about 1 ppm (depending upon mean daily temperatures) is based upon extensive and thorough epidemiological surveys which have shown about 60 percent less dental caries. Data on total fluoride ingestion from fluids and diet are sparse, and show appreciable variation. In nonfluoridated communities total fluoride intake usually ranges between 0.5 and 1.5 mg per day whereas in fluoridated communities total fluoride intake ranges between about 2 to 3 mg per day. In caries prophylaxis a fluoride *dosage* of 1 mg per day is used as a *supplement* in addition to the fluoride normally present in the diets in nonfluoridated communities. It should not be confused with the *concentration* of fluoride used for optimal water fluoridation. Based on the concentration of fluoride in urine and on the caries prevalence of the children, it is clear that Marin County in 1973 was not optimally fluoridated. Adjusting the *concentration* of fluoride to about 1 ppm in public water supplies is unquestionably a safe, effective, practical and economical measure in reducing one of the most prevalent diseases in our society—dental decay.

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Caries Prevalence, Efficacy and Safety of Water Fluoridation

Dental caries in the United States is an almost universal affliction, affecting 98 percent of the population. It is the most prevalent disease of childhood. By the time an average child reaches school (5 to 6 years of age), he or she has about five decayed teeth, and by 15 years of age, he or she has about 11 decayed teeth. Clinical surveys of the dental health of children living in California show that dental caries is a severe problem. Classical epidemiological studies on populations have clearly shown an inverse relationship between caries prevalence and the natural fluoride *concentration* in the drinking water; in other words, the less fluoride in the water, the more decay. Furthermore, controlled fluoridation of community water supplies to an optimal *concentration* (about 1 ppm in temperate climates) has been shown to be the most effective public health measure in reducing dental caries. Carefully conducted surveys repeated in many different cities in the United States and elsewhere have shown a 50 to 70 percent lowering in the caries scores as a result of water fluoridation. It should be emphasized that the dental benefits of water fluoridation are not limited to childhood. Adults who have continually consumed fluoridated water have lower tooth mor-

tality and less decay than the corresponding age groups living in a low fluoride area.

The safety of water fluoridation has been carefully documented in the literature.[1-3] Thorough medical examinations of the children accompanied both the Newburgh-Kingston and Grand Rapids-Muskegon fluoridation studies. No significant differences were found in health, growth and development between children in test and control cities. The Newburgh examination was detailed and included determinations of height and weight; tonsillectomy rates; onset of menstruation; bone density judged by x-ray studies of hands and knees; skeletal maturation; hemoglobin level, erythrocyte and leukocyte count; skin moisture, texture, color and eruptions, and results of urinalyses. The conclusion of this long-term pediatric study was that there was no indication of any systemic effects, adverse or otherwise, except for the reduction in caries from the use of fluoridated water.

Opponents of water fluoridation have raised the question of mortality statistics which provide only indirect evidence concerning general health effects resulting from the use of fluoridated water. A comparison of 32 pairs of United States cities which included 892,625 persons in fluoridated cities and 1,297,000 in non-fluoridated cities showed no significant difference in mortality between these two populations[4] (Table 1). The city of San Francisco began water fluoridation on August 25, 1952; there has been no significant change in the mortality rate from all causes during the last 20 years since that time (Table 2). No differences have been detected in the incidence of cancer of the thyroid, kidney, stomach, esophagus, colon, rectum, bladder, bone and breast for people living in communities with optimal compared to suboptimal fluoride levels.[5]

TABLE 1.—*Mortality Rates per 100,000 Population**

Death	*Fluoride Cities*	*Control Cities*
Heart Disease	354.8	357.4
Cancer	135.4	139.4
Intracranial Lesions	111.5	104.8
Nephritis	21.9	26.9
Cirrhosis of the Liver	6.6	8.2
All Causes	1,010.6	1,005.0

*Adjusted for age, race and sex.[4]

TABLE 2.—*Mortality Rate per 1,000 Population in San Francisco*

Year	*Death Rate**	*Year*	*Death Rate**
1951	12.3	1970	12.4
1952	12.2	1971	12.0
1953	11.8	1972	12.3
1954	11.5	1973	12.0
1969	12.4		

*Not adjusted for age, race and sex. San Francisco Department of Public Health, annual reports. Water fluoridation was begun in August 1952.

Clearly the most persuasive argument for the safety of water fluoridation is based on the health of communities where, for generations, the inhabitants have been drinking water with a natural fluoride *concentration* of about 1 ppm. Specific claims of any health hazards have been few compared to the extensive scientific and clinical findings regarding the safety of water fluoridation. Most claims of injury due to water fluoridation have been based on uncontrolled or poorly controlled observations which, when carefully evaluated, have been found unsupportable.[6]

Status of Water Fluoridation in the United States Generally and in California

By the end of 1974, over 100 million people in the United States were served by fluoridated water supplies, either natural or supplemented. This represents about 59 percent of the population using public water supplies. In California, at the present time, there are only about 4 million people receiving the benefits of optimal levels of fluoride in their drinking water. Most of the Bay Area communities (San Francisco, much of Marin County, San Mateo, San Carlos, Palo Alto, Newark, Fremont, Hayward, Martinez and Pittsburg) are already enjoying the benefits of water fluoridation. It is also gratifying to note that in the recent referendum held in Alameda and Contra Costa counties, the residents served by the East Bay Municipal Utility District voted in favor of water fluoridation. Los Angeles, the largest city in the state, is one of the few metropolitan areas in the country which has not yet fluoridated its water supply. It is to be hoped that this situation will soon be remedied, so that residents will no longer be deprived of this recognized public health and preventive measure.

Evaluation of Alternative Fluoride Administration

Because not all populations are served by communal water supplies, alternative methods such as ingestion of fluoride tablets or drops, or fluoridated milk, bread and salt have been tested. In addition, topical applications in the form of pro-

fessionally applied solutions, gels or pastes, and self-applied fluoride mouthwashes and fluoride dentifrices have been tested. Some of the alternative fluoride vehicles, when taken regularly, have reduced dental decay but have not given the *maximum* protection found with water fluoridation. This is readily understandable. For example, fluoride tablets are only ingested once a day, and because of excretion in the urine and deposition in the skeleton, fluoride levels in the plasma are rapidly reduced. Furthermore, because the tablets are usually swallowed, the level of fluoride in the mouth is quickly reduced.

With water fluoridation, each person receives multiple small amounts of fluoride, which acts both topically on the tooth surface as the beverage is ingested and systemically to be incorporated in the skeleton and also in the tooth structure. On the basis of efficacy alone, caries reduction by water fluoridation is approximately 60 percent, whereas caries reduction by fluoride tablets is only about half this amount (Table 3). Caries reduction with tablets has usually required strictly supervised conditions in classrooms during the school year. When fluoride tablets have been distributed for unsupervised use in the homes, it has been found that children do not take the tablets with the same regularity and, therefore, the caries reduction has been less. Fluoridation of milk has been tested in a few studies; however, much more clinical evidence is needed before establishing this route as a satisfactory one. Furthermore, there are distinct disadvantages because milk is ingested in relatively large amounts during the first two years of life, but then consumption decreases. The addition of fluoride to milk also creates logistic problems because of the large number of dairies compared to relatively fewer water utilities.

Topical application in the form of solutions, mouthwashes and dentifrices has been documented as reducing caries. Fluoride dentifrices, when used regularly, will give modest reductions in decay, but another important use of toothpastes is to aid in oral hygiene. The expected caries reduction by any of these topical routes does not reduce caries to the same extent as water fluoridation (Table 3), because topical applications only reach the tooth surface and are not incorporated in the tooth structure while it is being formed. Topical applications possibly have a role in preventive dentistry to supplement the caries protection of water fluoridation, but not to replace it.

Optimal Fluoridation and Dietary Fluoride Ingestion

Optimal fluoridation refers to that *concentration* of fluoride in the water supply which provides maximum protection against dental caries and enhances the appearance of the teeth with a minimum possibility of producing objectionable dental fluorosis (brown staining or hypoplasia of the teeth). Since the temperature of the environment influences the amount of fluids that people drink, the optimal concentration depends inversely upon the annual average of maximum daily air temperatures.[7,8] The United States Public Health Service has recommended for drinking water an optimal fluoride concentration between 1.2 ppm at average maximum daily air temperature of 50 to 53.7°F to 0.7 ppm at 70.3 to 80.5°F.[9] A more recent study was conducted by the Division of Dental Health, California State Department of Public Health to obtain precise data from which standards could be established in relation to mean maximum temperature for optimal *concentration* of fluoride ion in domestic water supplies.[10] More than 9,000 children (12 to 14 years old) in more than 100 communities were examined for dental caries and enamel hypoplasias. On the basis of this study the recommended optimal fluoride *concentration* ranges for three mean maximum temperature zones are 65°F and below, 1.1 to 1.3 ppm of fluoride; 66° to 79°F, 0.8 to 1.0 ppm of

TABLE 3.—*Cost and Efficacy of Fluorides in Various Forms*

Method	*Yearly Cost Per Child (Dollars)*	*Expected Caries Reduction (Percent)*	*Practicality*
Fluoridation of public water supply	.10-.20	60-65	Excellent
Fluoride tablets and drops	6-11	20-40	Poor (for home use) Fair (if given at school)
Fluoride mouthwashes	8	20-50	Fair
Fluoride dentifrices	2	15-25	Good
Fluoride topical application	12-24	30-40	Good

TABLE 4.—*Daily Fluoride Intake in Nonfluoridated Communities*

Age Group	*Dietary Fluoride (mg)*	*Water Fluoride (mg)*	*Total Fluoride (mg)*	*Comment*
Adult Male	0.16	0.30	0.46	Based on analysis of exact duplicates of all food and drinks of 1 subject over 20 week period[11]
	0.2-0.3	..	..	Based on *estimate* of an average diet[13]
6-14 weeks	..	..	0.10-0.17 Av. 0.14	Infants diet: milk formula only[14]
23-24 weeks	..	..	0.43-0.79 Av. 0.56	Selective diet, avoided tea and fish[14]
	..	.2 ppm	0.4-1.6	Linear correlation between caloric intake and total fluoride[15]
Adult	..	..	0.78-1.03 Av. .91±0.11	Analyzed hospital diets and beverages from 4 communities with water fluoride concentration 0.08 to 0.44 ppm[16]
5-6 years	..	..	0.94	Analyzed diets from selected daily food and beverage lists*
7-9 years	..	..	1.11	
10-12 years	..	..	0.91	
14 years	..	..	1.52	

*Elsewhere in this issue.

fluoride, and 80°F and above, 0.5 to 0.7 ppm of fluoride.

It must be emphasized (a) that the reduction in dental caries is related to fluoride *concentration*, (b) that water consumption is uncontrolled, (c) that fluoride ingestion also occurs from dietary sources and, therefore (d) that the total *amount* of fluoride taken into the body daily is highly variable. The question of how much fluoride is ingested from dietary sources, beverages and drinking water has been the subject of several surveys and considerable speculation.

In one of the earliest studies, exact duplicates of all food and drink consumed over a 20-week period by one young man living in a low-fluoride area were analyzed.[11] Total fluoride ingested was about 0.5 mg with almost twice as much derived from fluids as from the solid diet. Urinary and fecal excretion accounted for 91 percent of the total fluoride ingested. McClure[12,13] *estimated* that about 0.2 to 0.3 mg fluoride would be obtained daily from foods in a nonfluoridated community and about 0.3 to 0.6 mg from foods in a fluoridated community. At that time McClure wrote: "The amount of fluoride ingested in food seems also to be surrounded with considerable uncertainty." More recently dietary surveys, admittedly limited in scope, indicate that the total fluoride ingested in a nonfluoridated community is about 1 mg per day, but this is subject to considerable variation (Table 4).

TABLE 5.—*Relationship Between Fluoride Concentration in Drinking Water and Urine*

Number of Urine Analyses	*Fluoride in Drinking Water (ppm)*	*Fluoride in Urine (ppm)*	*±Standard Error of Mean*
35*	0.0	0.34	
8*	0.1	0.37	
8*	1.0	0.92	
42†	<0.1	0.32	.03
8‡	<0.1	1.44	.37

*Each analysis represents 11 to 28 spot urine specimens from 14- to 18-year-old boys.[17]

†Analysis of randomly collected spot urine specimens from 12- to 17-year-old boys and girls living in Marin County, performed by Department of Public Sanitation and Radiation Laboratory, State of California.

‡From children in Marin County, aged 6 to 14, receiving fluoride tablet supplements.

There is no convincing evidence that fluoride ingestion has increased in nonfluoridated communities as has been proposed by some antifluoridationists. In fact, the urinary fluoride concentration which reflects fluoride intake, was 0.32 ppm for children living in Marin County before water fluoridation and was remarkably close to the level of 0.34 to 0.37 ppm reported almost 30 years ago in communities with 0 to 0.1 ppm fluoride in the drinking water[17] (Table 5).

Data on the fluoride content of diets in a fluoridated community are shown in Table 6. Foods cooked in fluoridated water tend to pick up additional fluoride. Total fluoride ingested varies with age and choice of food items, generally ranging between 1.7 to 3.4 mg with a mean of about 2.5 mg per day for adults. Fluids account for about 60 percent of the total fluoride ingested; the remaining 40 percent comes from the solid foods themselves and water used in their preparation.

Tables 4 and 6 indicate appreciable differences

TABLE 6.—*Daily Fluoride Intake in a Fluoridated Community*

Age Group	*Dietary Fluoride (mg)*	*Water Fluoride (mg)*	*Total Fluoride (mg)*	*Comment*
1-12 years	0.03-0.27	0.39-0.56	0.42-0.82	Based on *estimates* of water consumption and caloric requirements[12]
Adult	1.0-2.0	fluid approx. 1.6	2.6-3.6 range 2-5 mg	Food fluoride increased approximately 0.5 ppm if processed in fluoridated water. Total fluoride intake based on *estimate* assuming 1-2 mg dietary fluoride[18]
Adult males, 30-50	.. ..	.. ..	3.57-5.37 Av. 4.39	Patients were *not* in fluoride balance. There was positive fluoride retention (+1.39 mg) and urinary fluoride level (approximately 1.7 ppm) was elevated. Implies that hospital diet was atypical[19]
Young persons ...	...	..	0.65-2.25	Linear correlation between caloric intake and total fluoride intake[15]
Adults	...	..	1.30-2.90	
Males, 16-19	0.8-0.9	fluid 1.3-1.5	2.1-2.4	Analyzed a two-week "market basket" food survey[20]

of reported total fluoride intake. In part, this may be due to the diets themselves, which have included meals from private homes, hospitals, restaurants and market-basket samples. Some analyses have included all fluids ingested; other reports have only *calculated* the fluoride derived from liquids. Some of the studies are based not on analysis of actual meals but on *estimates* of the fluoride content of specific foods. Considering all the different approaches in sampling and determining dietary fluoride, such variation is not surprising. More accurate and detailed information on fluoride intake levels in the population is needed.

Discussion

Lee reports (in this issue of the JOURNAL) that the total fluoride ingested by a select group of children in Marin County before water fluoridation was between 0.35 and 2.2 mg and that averages for the age groups 5 to 14 ranged from 0.9 to 1.5 mg. These values were higher than he had anticipated and in his opinion fulfilled "previously accepted criteria for optimal fluoridation." Of the 153 records of single day diets, Lee chose "by chance lot" 17 for fluoride analyses; these had been submitted apparently by only four families. Careful examination of these diet histories showed that clams, tuna and tea comprised a part of the diets, especially of Family C. Sea foods and tea are well known for their relatively high fluoride content and this may well explain these data.

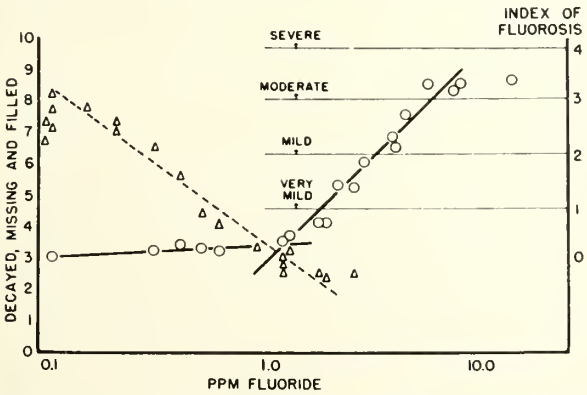

Chart 1.—Relationship between fluoride *concentration* of the drinking water, expressed in parts per million (ppm), caries prevalence measured as decayed, missing or filled teeth (Δ---Δ) and dental fluorosis (0—0).

However, a more important question that has been raised is that of *optimal fluoridation*. This is defined in terms of *concentration* of fluoride in the water which in Marin County because of its climate should be 0.9 to 1.1 ppm. Optimal fluoridation is *not* defined as fluoride intake in milligrams. The great body of data on which water fluoridation is based shows beyond reasonable doubt that dental caries decreases as the water fluoridation *concentration* increases up to between 1 and 2 ppm (Chart 1). Water intake in Dean's classical studies was uncontrolled and presumably variable. The extent of reduction of caries was related only to fluoride *concentration* regardless of the *amounts* of fluoride taken in food or water. The "accepted criteria for optimal fluoridation" relate only to *concentration* in community water supplies. It is patently fallacious to suggest "that Marin was an optimally fluoridated community without the addition of supplemental water fluoridation."

The urinary fluoride concentration of Marin children before water fluoridation was definitely

suboptimal. A survey of the caries prevalence, expressed as decayed, missing or filled permanent teeth (DMFT) of 6- to 14-year-old school children was conducted by the Marin County Dental Society in 1973 before water fluoridation. At every age level, the children in Marin County had significantly more decay than those living in communities whose water supplies had been optimally fluoridated (Table 7). The data on the caries prevalence among Marin County children is limited in scope, particularly at ages 8, 9 and 14. Nevertheless, the trend of higher caries in Marin County is obvious and approximates the caries prevalence in other nonfluoridated communities in North America.[22] There have been, of course, many extensive surveys of caries prevalence in optimally fluoridated communities that produced results very similar to those found in Providence. The data from Providence are cited primarily because that survey was conducted at about the same time as the one in Marin County. Substantial reductions in dental caries following fluoridation have now been reported in many different communities in the United States and throughout the world. The consistency of these findings, namely a 50 to 70 percent caries reduction, among populations living under diverse environmental and cultural conditions is most impressive.

It is regrettable that Lee has confused *dosage* of fluoride supplements with the optimal fluoride *concentration* in the drinking water, which is well established. A separate problem is to furnish fluoride to children where there are no communal water supplies. A conservatively safe *estimate* of 1 mg fluoride per day for children 3 years of age and older is widely used for *supplementation* in communities with negligible amounts of fluoride in their drinking water. This dosage is drawn from rule-of-thumb average water consumption figures and does not take into account fluoride ingested from foods.

TABLE 7.—*Comparison of Prevalence of Decayed, Missing and Filled Permanent Teeth (DMFT) in Marin County with an Optimally Fluoridated Community*

	Community			
	Marin County <0.1 ppm‡*		*Providence, Rhode Island† 0.9-1.1 ppm‡*	
Age	*Number of Children*	*Mean DMFT/Child*		*Number of Children*
6	150	1.0	0.4	401
7	162	1.1	0.9	813
8	19	2.1	1.2	1,285
9	8	2.0	1.5	2,032
10	163	2.7	1.8	2,407
11	187	3.1	2.1	2,815
12	202	5.0	2.6	3,740
13	229	5.1	3.1	4,349
14	18	7.6	3.8	3,976

*Dental survey conducted by Marin County Dental Society in 1973 before water fluoridation.

†Data from Providence, Rhode Island in 1972-73 after 20 years of water fluoridation.[21]

‡Water fluoride concentration.

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Special Article

An Anti-Intellectual Movement in Medicine

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IT IS NOT NEWS that Western man is reentering a climate of anti-intellectualism—a new Dark Age wherein some fight fear with long since discarded devices. We have witnessed the return of mysticism as reflected in the reemergence of the black and white magic of the Tarot, the simplistic nonsense of astrology and a wave of perfervid religiosity. If these methods had ever worked, they would not have been reassumed and discarded myriad times in the history of civilizations.

We are in a state of chaos, but it is nonsense to blame the mess on the clean, flourishing, logical and technical disciplines of science. Rather, it is, once again, the lagging of practical humanism reflected in failure of social and political systems to implement scientific knowledge that has created a gestalt inimical to the health of the individual person and, therefore, to the health of society. And I fear the wave of anti-intellectualism has begun to encroach upon the borders—if not the heart—of medicine.

Let me explore this.

One year ago I was battling the problems of providing patient care in an urban-rural community, with night calls, house calls and all the joys and agonies attendant thereto. And one cannot obliterate certain perspectives and attitudes simply by switching chairs: in this case, to one behind an editor's desk. So I would like to ruminate some things that had begun to worry me before; and now that I have come to the big city and begun to wander about, and to take the pulse of American medicine, the fears have begun to crystallize.

First Signs of Change

It is a little like watching animals react to a small fire in the forest. The whiffs of smoke were detected by sensitive creatures about five or ten years ago. You are all familiar with the tremors that were felt by the academic community. Some whispered that our research and educational establishments had become badly out of joint with the times. There were murmurings about excess fat in research budgets, escalating costs of medical care and maldistribution of professional talent—geographically and socioeconomically. But just as you and I had, the bright young graduates of the 60's continued to swarm the ivory towers and populate the specialties, while the vast mass of patients—those who were less-than-violently ill or less-than-interestingly ill—were all but forgotten in the academic scramble. And all of this had significant fallout.

Patients obliged to wait several hours in offices, clinics and emergency rooms agreed most readily when they were told we were in the midst of a doctor shortage. And for many lower and middle income groups good medical care was scarce, if not unknown. The news media were replete with stories of dramatic progress in the science of medicine but little of this was perceptible, little filtered down to the vast mass of the less affluent sick. Words such as relevance and social responsibility began to creep into the conversations of our medical young.

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Meanwhile, many medical schools, still basking in the warmth of their post-Flexner era bonanza, began to sense the distant smoke, and some reacted. Incoming classes were doubled and tripled; selection committees reached out for minority group students; curriculum committees sought new dimensions. Schools with unfamiliar names mushroomed throughout the land.

Some clinical teachers became concerned about the capability of the existing, relatively finite pool of medical educators to accommodate the surge of new students, and still maintain traditions of excellence in classroom and clinic. But these fears were assuaged with assurances that the new mass media techniques would facilitate clinical teaching. Yet some of us were still worried about relegating these critical responsibilities to mechanical surrogates. But our concerns were only small eddies swirling against the mainstream.

More Doctors, Faster

Produce more doctors and do it faster was the watch word. We were advised that we were 30,000 doctors short throughout the country—but few stopped to analyze this figure as it related to distribution and specialty. Yet on the basis of gross numbers alone the gates were thrown open to foreign-trained physicians, and they came in droves—to fill the need. This is not the time or place to discuss the merits or debits of this most complex situation. But the fact is that this relaxed policy of medical immigration did little to take the pressures off American medical schools.

Thus, to accelerate the production of warm medical bodies, many medical schools condensed the curriculum by emasculating or deleting "irrelevant" departments (clinical pharmacology was an early, costly casualty); some merely eliminated vacation periods and began to churn out graduates in 36 months. Not much time for reflection, or emotional growth, or evolution of the other intangible elements that go to make up that elusive quality we call medical maturity.

No one seemed to ask "What is the hurry?" Also no one paid much attention to where the warm bodies, foreign and domestic, gravitated. And there was no perceptible change in the pattern of physician distribution—geographically or by specialty. No one faced the problem of "How are you gonna keep 'em down on the farm—after they've seen Parec" or, to paraphrase, "How are you going to keep 'em down on the Indian reservation, or in the horizontal ghettoes of the delta, or the vertical ghettoes of Detroit after they've seen Massachusetts General or the National Institutes of Health or Scarsdale or San Francisco or Maui?"

And what about the graduates of the late 50's and 60's?

Some of us anachronistic curmudgeons—erstwhile bedside clinicians—could be heard to mutter darkly about the new breed of graduates and their tutors, mechanical and otherwise. Nasty phrases like laboratory-oriented myrmidons, molecular biology buffs, disease rather than patient-oriented, bereft of human virtues, assembly line products crept into our cloakroom conversations.

Yet, the first significant militant protests against the educational grist mill came from the students. It was their forthright demands for relevance in curriculum and for meaningful medical experience that arose in response to their expanding social awareness. Students—not teachers—were the ones who scrutinized the academic tradition which had taught disdain of the local medical doctor, the LMD, and had extolled the virtues of the investigative-teaching career pattern. Students were the ones who studied this philosophy—and found it lacking, out of balance, out of synchrony with the times. While our generation focused mainly on individual patients, and accused our immediate successors of looking mainly at disease mechanism, indeed recent graduates were the ones who looked beyond both—at the *need of society.*

There is a requirement that all three aspects—patient, mechanism and society—be kept in mind, and they are not mutually exclusive. But it is a difficult balance to strike. However, the point had been made.

Admittedly, many perceptive educators had already began to suspect that perhaps the post-Flexner momentum had crested, and that under their stewardship the thrust of medicine had carried beyond its cardinal purpose—the care of patients. They began to realize that concepts of patient care had become lost, sidetracked somewhere in the fascinating catacombs of scientific methodology. Educators began to realize that through their teaching, diseases had replaced patients in the priorities of education in medicine.

An Awesome Body of Knowledge

But one must not forget; the smoke in the forest had originated in a most remarkable crucible. The golden years of research and postgraduate clinical

training that began after World War II had produced an incredible cadre of talent and an awesome body of knowledge. New pathophysiologic mechanisms had been identified. Dramatic discoveries in molecular biology, immunology, cytogenetics, and enzyme and hormone chemistry had occurred. New diagnostic techniques and therapeutic tools were devised. All were products of these marvelous years.

This was reflected in gigantic growth in capability for quality patient care. Admittedly, the distribution and availability of this care were far from optimal, however—as I said earlier—social and economic implementation always lags behind advancement in sciences. But the capability was there. (I sometimes suspect that in the grand scheme of life, there are times when such sudden spurts of genius and productivity must occur to maintain viability. But always, something else must be sacrificed.)

Thus, despite this flush of success in science, some of us felt that during these grand years of progress in hard science, something had been lost along the way. Perhaps it was that bedside senses were being neglected and were becoming dulled. We thought that some training programs were out of balance; there was too much mechanization; too much stress on nuts and bolts—too little stress on people. In the passionate effort to master the vast new knowledge, students were being deprived of something vital and wonderful and satisfying in medicine: the joy of eyeball-to-eyeball, personal, one on one, longitudinal communication with patients. The humanity of medicine was all too often shunted aside in the headlong pursuit of hard science. There was more to be learned, and less time to learn it. Something had to be sacrificed, and we felt the choice, although it was perhaps inevitable, was unfortunate. In many cases the art of medicine was left on the curriculum cutting-room floor.

But the smoke in the wind became even more perceptible about three or four years ago. Things began to shift back toward the bedside. Preceptorships, neglected for 25 years, were being rediscovered. Most clinicians viewed this with cautious pleasure. A balance was being struck between bench and bedside. But in recent months, my delight has begun to fade. It has been replaced by something close to alarm. Let us look at what is happening.

We are told by people who should know that despite the current overall physician shortage, if present trends continue (the production of our medical schools plus the continued influx of foreign medical graduates), within 12 years the United States physician pool will number between 495,000 and 520,000. By 1985 we will have 220 doctors per 100,000 population as compared with 160 in 1970. If you believe this projection (and this numbers game has been the subject of great debate) we are facing a doctor surplus.

Listen to the words of Dr. Charles C. Edwards at the Association of American Medical Colleges meeting in 1973, "I think that clearly we have moved beyond the point at which concern about a shortage of physicians was genuine if somewhat exaggerated. Even more significant is the possibility we may well be facing a doctor surplus in this country." Later he said "The task the medical schools now face is to work toward solution of problems that relate not to aggregate numbers of physicians, but to specialty and geographical maldistribution, physician productivity, and the underrepresentation of women and minorities among the health professions . . . "

The Government and Medical Education

This can be translated into the fact that the government is taking a hard look at its philosophy of financing medical education. The holders of the federal purse strings are not satisfied with the current efforts by medical schools to meet the practical needs of the citizenry. Another example: There was a bill (S-3585, Kennedy-Javits) which was approved by the Senate Labor and Education Committee. In its original form it would have provided almost 2 billion dollars over a three-year period in federal aid for medical and other health profession schools. This bill would have given the federal government power to allocate and limit postgraduate training for physicians. It included a provision designed to curb the reliance on foreign medical graduates and to increase the number of primary-care physicians. It would have required the Department of Health, Education and Welfare to limit the number of postgraduate training positions in hospitals to no more than 10 percent above the total of domestic medical and osteopathic school graduates of that year, and to assign the total number of physicians to various categories of specialty and subspecialty training.

Among other provisions of this bill were those that would require all young physicians to serve for two years in a sort of domestic peace corps

program, whether or not they received federal loan or scholarship help. Also, within two years the Department of Health, Education and Welfare would establish national standards for licensure of physicians and dentists. Under this bill, licensure renewal would occur at least every six years. A physician or dentist licensed to practice in any state would qualify in any other state in which the national standards are in effect. If a state had standards exceeding the national standards, a physician coming into that state would have to meet the additional requirements.

Thus it was designed to require all recent medical graduates to serve in shortage areas, to limit the number and variety of postgraduate positions and to ensure the relicensing of all physicians. The final, much modified version—as amended by Beall of Maryland—was passed on September 24 by the Senate, 81 to 7. It would provide federal aid to medical and dental schools that agree to allocate 25 percent of their classroom spaces for students volunteering to serve in urban slums or rural areas short of medical care workers. In return for their service, the students would be entitled to government scholarships. The bill would require one year of service for each year of scholarship aid.

To say the least, all of this is most provocative —and I will not speculate upon it at this time. Suffice to say that it is perhaps an indication of what is in the wind, a cardinal demonstration that the government is indeed concerned about problems of contemporary medicine in America at all levels. And I will not speak of the implications of Professional Standards Review Organizations, Health Maintenance Organizations or national health insurance on medicine overall. But let us return to the problem of medical education.

New Educational Directions

In an effort to anticipate this need to qualify for such federal support of medical education, many schools have reevaluated their priorities in curriculum planning. One major thrust of all of this has been the creation of departments of family medicine—a welcome, long overdue development. The popularity of these programs is evident through the progressive increase in positions and applicants over the past three years. One estimate by the Division of Manpower Intelligence places the current shortage at 27,000 to 30,000 family-care physicians such as general practitioners, internists, pediatricians and obstetricians. So evidently there is a long way to go to meet the current need in numbers—as well as in distribution.

But in recent months have experienced a dim sense of uneasiness. I have detected a subtle anti-intellectual, antispecialty, antiresearch movement developing at several levels, and it is expanding. Some might say that we had it coming—after years of pejorative comment about the LMD on our wards and in our clinics. Yet, while we all advocate more family physician training, I can see no useful or rational purpose in denigrating investigative or specialty medicine, while pursuing this new venture. I have heard such things as "students with good science grades do not necessarily make good doctors." This may apply to some few, but it is the implication of the statement that is disturbing. It has an anti-intellectual ring. No one can deny that there is a need in the selection process to seek out students who have qualities of compassion and human warmth. Also this aspect of personality must be nurtured and encouraged during the years of education in medicine, yet one must not ignore the seminal importance of a firm foundation in the sciences.

Human compassion and academic excellence are not mutually exclusive virtues. Some of us are egotistical enough to think that we have come close to this ideal. And we are many.

This is not a time for intemperate generalizations; these are indicators of panic and reaction. It is the time for balance—rational creative planning and the initiative should come within the profession.

It is encouraging that many of our medical young are highly motivated to family practice. And we do need more of them. Yet we must continue to produce a proper proportion of specialists and investigators to complement the health care team.

And I must express my concern that government through its fiscal power over medical education is seeking means to control the input into medical specialties. It is antithetical to traditional American freedom of choice for government to exercise control over one's selection of his life-work. Yet unless medicine itself can solve this problem of specialty growth and distribution, it may well become a function of government. As I look ahead 10 to 20 years, my crystal ball becomes distressingly cloudy.

Improving Physician Distribution

The problem of physician distribution is admittedly difficult, but I do not think it is insurmountable. There are several possible options. Federal subsidy of students with a mandatory two year pay-back time is one possible solution. But again the implication of universal compulsory service has ominous overtone. And, parenthetically, I might add that if indeed this comes to pass for medicine, why should we be singled out? Why not dentists and lawyers and teachers and perhaps even engineers, architects and plumbers? Certainly these services are also maldistributed throughout the country. But I am wandering; down this catacomb lies madness.

Also regarding distribution, I am convinced that there are many physicians who can be induced to care for patients in less desirable geographical areas. This can be done by a reorientation of philosophy and priorities, by offering a rewarding lifestyle, by a team approach, with perhaps three or four family-oriented physicians working in a group each trained in a different discipline—internal medicine, obstetrics-gynecology, pediatrics.

There must be professional recognition by colleagues and an end to the denigration of the LMD. There must be realistic financial compensation and rapid access to specialist backup. These physicians must also be provided a practical continuing medical education program, perhaps through periodic sabbaticals, while they are replaced by someone of comparable background and training.

It is beyond the scope of this discussion to consider the role of physician assistants in this plan. But their potential contribution to patient care in remote areas and in other sections where physician distribution is a problem, is another distinct aspect to the solution of the distribution dilemma.

Changes in Investigative Medicine

Now let us talk about what has happened in investigative medicine. It was about seven years ago that we began to hear new words such as targeted research and goal-oriented investigation —words sprung from the lexicon of the bureaucrat. It epitomized a pragmatic philosophy that seemed to say, "Trap the brightest investigators you can find; lock them in a laboratory with the finest equipment and limitless resources; feed, water and pet them occasionally. And if you keep them there long enough, they will find cures for cancer, heart disease and stroke."

Well, timetables may be applied to mathematical and physical sciences. And the pharmaceutical sciences have been successful in the creation of new molecules through a goal-directed orientation. Propylthiouracil and several synthetic antibiotics (most notably rifampin) have resulted.

But biological arts do not work this way. In medical research there is, unfortunately, one variable that cannot be manipulated: the patient. The myopic bureaucratic philosophy that seems to say "If we can get to the moon in ten years—certainly we can cure cancer in 15," was implemented through various mechanisms resulting in a significant constriction of research funds, most of which were diverted from "non-goal-oriented research." The alleged fat was trimmed mercilessly. Those who could not be enticed or coerced into "target-oriented" research began to drift away. It is probable that a significant portion of one or two generations of young investigators has already been lost. It is a tragedy of dimensions that may never be fully appreciated, since it cannot be measured. How do you evaluate something that was never discovered?

Throughout the history of art and science there have been some free spirits that cannot be tethered. They must be recognized, cherished and given their heads. These have always been our most creative people; this is the nature of art and science. Alas, it is a concept alien to the bureaucratic psyche.

And how much progress have we made in the war against heart disease, stroke and cancer? We are still a nation of slaves to cultural indolence; we are overindulgers in food, alcohol and cigarettes, and underindulgers in exercise, seat belts and self-restraint. No magic bullets have been forthcoming; no earthshaking breakthroughs from those looked into target-oriented research programs. There is statistical indication that there has been some reduction in the deaths from myocardial infarction over the past five years. And some have related this to a more rational diet among American men. But aside from this glimmer of light, there is little evidence of success in other areas.

Too often, solutions of medical problems are inextricably interwoven with cultural, social and economic phenomena. As all of us know, quite often major discoveries are the result of serendipitous observations in disparate disciplines—

seemingly unrelated—small discoveries made by bright, independent, non-goal-oriented people who just happen to meet and chat on boardwalks or in coffee shops.

Continued Support for Basic Research

There is an urgent need for continued support of investigation in basic science and clinical research. Perhaps investigative medicine should not be as unstructured and insensitive to fiscal reality as in the past, but there must be a mechanism for recognizing and encouraging investigative virtuosity. This is the heart blood of medicine—the source of new knowledge.

We must not overreact by a return to pre-Flexner attitudes—just as we must not continue an unrealistic spiral into superspecialties at the expense of primary care physicians. I will repeat —there is need for balance.

I believe there will always be room in medicine for men and women of talent and dedication, and I think this essential freedom can be preserved without limitation of professional options as seems to have occurred in England and Sweden. And I repeat—I fear the incursion of government into this seminal aspect of medical education—as it fills a vacuum—a void left by the indolence and indifference of medicine.

Human Investigation and Morality

Finally, one other area deserves comment. The third direction of the anti-intellectual fire in the forest is human experimentation. This unfortunate expression seems to conjure up images of Buchenwald. I will confine these remarks to research on humans, the problems of abortus research, use of materials derived from human sources and animal investigation would carry us far into the night. But let us talk about human investigation.

No rational person will deny the virtues of a sensitive but rational protocol review committee. And there have been lapses in our vigil to protect human individual rights. But I submit that most often these lapses have been caused by carelessness, or overwork, or overenthusiasm rather than by callousness. There are exceptions.

No matter what semantic gambit one may wish to employ, we are all in the business of caring for human beings. Therefore, we must learn about human beings. And in the final analysis, I know of no other way to do this than to try procedures and therapies with human beings. To extrapolate to the absurd, each time we treat a patient with an approved drug or submit him to a well-tried surgical procedure, it is indeed a miniature human experiment. We speak of a risk-benefit ratio—this is itself a euphemism for human experimentation.

It is a truism that every significant advance throughout the history of medicine has been based on human experimentation. One wonders how Pasteur, Koch, Jenner, Reed, Florey and hundreds of others would have fared at the hands of some protocol review committees? And should they have been permitted to do such studies? Were they less moral, less sensitive? Was life worth less?

It would seem that at some periods in history the rights of the individual person weigh more heavily than those of society. Then the pendulum will swing again. The dilemma is this: protection of the rights of the individual balanced against the good of mankind. *Is there ever an occasion when the civil liberties and moral rights of an individual can be set aside to achieve a greater good?* Answer that, and all other factors fade into insignificance. It is impossible to generalize. Must we begin to think in terms of lesser morality and greater morality? What is our moral obligation to women with breast cancer now, who might be tested with a drug that may arrest the tumor, but may have significant toxicity—as opposed to our moral obligation to untold future generations of women who we know will die of breast cancer? How does one measure the morality of present risk against future benefit? Clearly, it would be immoral to stop research in cancer, stroke and heart disease.

And who are to be the volunteers who provide informed consent (that nightmare of social, economic, psychologic and legal entanglement which defies universal definition)? Should the volunteers be restricted to research scientists? (Well, surely in this group there could never be a question about full awareness of present risk or full cognizance of possible future benefit.) Are we ever justified in the use of children (How do you inform a child?); can a parent give consent for a child? How about prisoners (whose situation always might be construed as intrinsic coercion)?

As an aside, after publication of a recent editorial in *JAMA*—an eloquent plea to protect prisoners—we received several letters from prisoners who expressed anger and frustration—at the possible restriction of their rights as human beings to volunteer for medical research projects—in an effort to square themselves with society or

to indicate their desire to cooperate with society or even just to earn extra money and privilege. So there is never black and white—in any situation.

And how about using the mentally retarded (who may certainly be incompetent to give informed consent)? Are we justified in using any of these groups of persons who are less likely to make a contribution to society than are research scientists? And who is to make such a judgment?

I pose to you an insoluble dilemma. All one can ask is that each situation be studied with consummate circumspection and be approached rationally and compassionately. Again I am not convinced that ironclad guidelines, even etched in tablets from on high, will solve the problem.

One might say that no person has the right to involve another person in an experiment that could maim or kill, regardless of the desire of the volunteer or the probable benefit to mankind. And this is a debatable point. It has more shades of gray than a charcoal drawing.

Yet, we cannot let progress in medicine grind to a halt in a backlash of neurotic guilt and sanctimony. You know it has become almost fashionable—a herd instinct—for anonymous referees of medical manuscripts and rare, timorous journal editors to respond to papers that include the use of human volunteers (in almost any context) with pharisaic castigation—hurling thunderbolts from Helsinki—to vilify the investigators. To me, this is destructive, purposeless sophistry.

Thus, I submit, it is time to stop and take inventory.

The Three Cardinal Issues

Some may say I have erected three men of straw—hobgoblins of my own nervous invention. I hope this is true. But in my opinion postdoctoral education, research in general and human experimentation are cardinal issues, at risk in the present and in the foreseeable future.

I believe we stand at a major impasse. I see a vast swampland of intellectual impoverishment in medicine looming ahead. Yet scattered throughout I see tender saplings of what could become a magical forest destined to flourish and bring the bounteous blessings of an improvement in the quality of life to all of our people.

So we must select our options with prudence and circumspection. If we do less, if we falter and despair, one day we may all awaken clutched in the doughy embrace of pervasive mediocrity. And so I say let us look to the forest.

Let us approach the future with courage, born of the conviction that man is a most remarkable creature—capable of rising to the need of the hour, capable of inspiration to solve his problems with vision and tenacity and practical genius. These have been the hallmarks of our species.

Information

Inhalation Therapy

Joint Accord on the Role of Respiratory (Inhalation) Therapy Personnel in Airway Management and Endotracheal Intubation endorsed by the California Medical Association, the California Hospital Association, the California Society for Respiratory Therapy, the California Society of Anesthesiologists and the California Thoracic Society

THE FIRST STEP in resuscitation from cardiac arrest, respiratory failure or acute airway obstruction is the establishment of a patent airway. This usually involves positioning of the patient and the use of an artificial airway inserted through the mouth or nose into the pharynx or trachea. Removal by suctioning of inhaled or obstructing secretions or vomitus is frequently necessary.

In the hospital situation teams of health personnel, i.e., nurses and respiratory therapy personnel approved by the hospital medical staff, are trained to respond to emergencies and take responsible action in the absence of a physician. If a suitably trained physician is present, he will take charge of the emergency situation. In his absence we recognize the propriety of having specially trained and authorized personnel perform the necessary steps involved in respiratory resuscitation if the following requirements have been satisfied:

1. A procedure is established and adopted by the medical staff of the hospital.

2. A suitable training program in resuscitation and emergency airway maintenance is established and conducted by a physician or physicians appointed by the medical staff for members of the resuscitation team.

3. Personnel who satisfactorily complete the training program and demonstrate competence shall be certified by written documentation. Such documentation will be kept in their personnel files.

June 18, 1974

Refer to: Kahn FH, Visscher BR: Water disinfection in the wilderness—A simple, effective method of iodination (Information). West J Med 122:450-453, May 1975

Water Disinfection in the Wilderness

A Simple, Effective Method of Iodination

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BEFORE WORLD WAR II, when backpacking and foreign travel were less common, the traveler gave little or no thought to water contamination. It was assumed that mountain streams were pure. With improved surveillance it is known that most streams of the United States are polluted.[1] Waterborne disease continues to be important in undeveloped areas, here and abroad,[2-4] though in urban areas of the United States it is uncommon. Reliable data on the incidence of waterborne disease among travelers are not available, yet potentially waterborne diseases including Salmonella infections, amebic dysentery, giardiasis and infectious hepatitis are commonly observed among travelers returning from abroad and from remote areas of the United States.

The authors' interest in water disinfection was sharpened when they acquired giardiasis after drinking from a partly frozen stream on the Long Valley trail to Mount San Jacinto, California. At this time in early May 1971, human habitation of the area was sparse, and snow covered the ground. Cold weather is no protection from intestinal parasitism, and may present a problem in water purification, as will be explained later.

A water disinfectant must be able to kill the hardiest of each group of organisms, especially amebic cysts, which are hardier than their active forms, and enteroviruses, the most resistant to

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disinfection of the pathogenic microorganisms. At the same time, the toxicity of the chemical must be very low compared with its germicidal potency. A water disinfectant for the traveler presents special requirements which are of less importance to the municipal water sanitary engineer. These include simplicity, effectiveness in the presence of nitrogenous pollutants, rapidity of antimicrobial action over a wide pH range and immediate palatability. The backpacker will, of course, demand light weight.

Iodination meets these requirements,[5-7] and offers a number of advantages over the time-honored chlorination[8,9] of small quantities of water with p-dichlorosulfamoyl benzoic acid (Halazone®).

During World War II, Halazone was issued for individual use when other forms of water treatment were not available. Though Halazone produced potable water in the absence of heavy contamination, its efficacy in treating cold, heavily polluted water containing resistant forms such as viruses and amebic cysts was seriously questioned. In 1942, at the request of the armed forces, investigators at Harvard University initiated a search for a more dependable technique of water sterilization. This study recommended the use of iodine for treatment of small quantities of water. A technique for iodination was developed and adapted by the armed forces.[10] Subsequent investigations confirm the superiority of iodination as a personal water germicide, yet Halazone continues to be widely used and is currently the only commercially available agent for this purpose in Southern California.

Chlorination

Chlorination by Halazone in the recommended dose depends on the slow release of 2.8 parts per million (ppm) of free chlorine for its immediate antimicrobial action.[11] Chlorine under ideal conditions, namely a pH of 7 or lower and the absence of nitrogenous compounds, hydrolyzes to hypochlorous acid (HClO). The highly active HClO is an excellent germicide.[12,13] The high reactivity of HClO is its main defect as a personal water disinfectant, since in the presence of amino and ammonia ions HClO is quickly converted to relatively inactive monochloramine.[14] Above pH 7 HClO hydrolyzes to the less active hypochlorite.

These two problems are solved in water purification plants by the practice of breakpoint chlorination. Breakpoint chlorination is the application of sufficient chlorine to bind with the organic materials in the water, while leaving a biocidal residual of free chlorine. But this technique requires continual testing and is not practical for rapid treatment of small quantities of water. The individual traveler must resort to simple chlorination, the practice of adding a fixed dose of a chlorine compound to water of uncertain quality. Simple chlorination is unpredictable,[15] and may be useless against bacteria[16] and enteroviruses[9,17] when water is contaminated with organic material.

A number of waterborne disease outbreaks have occurred when simple chlorination was practiced.[18] Neefe's classic study of an infectious hepatitis epidemic demonstrated the failure of combined chlorine to inactivate the hepatitis virus.[19] Enteroviruses were recovered from chlorinated tap water in Paris when breakpoint chlorination was not practiced.[20]

Additional disadvantages of Halazone are slow solubility and a short shelf life of five months when stored at 32°C (89.6°F). Potency is reduced 50 percent when stored at 40° to 50°C (104° to 122°F),[21] the temperature range one might expect in an automobile glove compartment on a summer day. Halazone loses 75 percent of its activity when exposed to air for two days.[22]

Iodination

Iodination, in contrast, with a weak aqueous solution of 3 to 5 ppm of elemental iodine (I_2) will destroy amebae and their cysts, bacteria and their spores, algae and enteroviruses at 25°C (77°F)[4] in 15 minutes or less (see Chart 1).[4,7,8] At near freezing (3°C, 37.4°F) disinfection will require 20 to 30 minutes at the same concentration of iodine, since germicidal potency is roughly proportional to temperature. Elemental iodine does not react readily with ammonia and amino ions, and therefore will remain an effective disinfectant in water polluted with nitrogenous wastes.[7,8] Iodine is effective over a wide pH range, hydrolyzing at pH above 6 to hydroiodous acid, which is a faster virucide than I_2.[8]

Iodination can be accomplished in three ways. One method is the addition of eight drops of 2 percent tincture of iodine to a quart of water, but this results in water of less than acceptable palatability.[22] A second is the addition of a tablet of Globaline® (tetraglycine hydroperiodide) to a quart of water, releasing active iodine in a con-

centration of 8 ppm. Globaline tablets lose 20 percent of their effectiveness when stored in sealed bottles at 75°C (167°F) for 24 weeks. They lose 33 percent of their initial activity when exposed to air for four days.[22] The third method, described below, using crystals of elemental iodine, has been recommended for treatment of water supplies of villages in underdeveloped countries,[8] but has not been previously described for use as a personal water germicide.

Procedure for Iodination Using Crystalline Iodine

The only equipment needed for iodination with crystalline iodine is a one ounce clear glass bottle, with a leak-proof bakelite cap, containing 4 to 8 grams (or any small quantity) of USP grade resublimed iodine (I_2). The bottle is filled with water and capped, shaken vigorously for 30 to 60 seconds, then held upright for a few moments to permit the heavy iodine crystals (specific gravity 4.6) to fall to the bottom. The iodine crystals are not to be used directly. Disinfection is accomplished at 25°C (77°F) by the addition of 12½ cubic centimeters (cc) of the near saturated supernatant iodine solution to one liter of water, to achieve a final concentration of 4 ppm iodine. Since the concentration of the saturated iodine solution varies with its temperature (see Table 1), only 10 cc of iodine solution would be needed if the bottle were kept at body temperature. At near freezing, 20 cc of iodine solution would be used per liter. (The cap of the iodine bottle may serve as a measuring device.) After a contact time of 15 minutes, the water is disinfected. When more disinfected water is desired, the above steps are repeated almost 1,000 times without replenishing the iodine crystals. The shelf life of crystalline iodine is unlimited. Under usual circumstances, a 2 ppm iodine solution with a contact time of 40 minutes would offer improved palatability and effective disinfection.

If increased germicidal potency is necessary because the water is turbid, cold or known to be heavily contaminated, the concentration of the iodine solutions could be increased to 8 ppm, with a contact time of 20 minutes.[5] However, in the interest of palatability, one may prefer not to increase the concentration, but instead increase the contact time (see Chart 1).

A clear glass bottle is recommended for the above procedure to permit observation of the iodine crystals. Plastic bottles of all types take on an opaque brown stain after long exposure to the working solution. Further, plastic bottles tend to leak as one travels to high altitude, and distort and crack on descent to low altitude.

By all measures, the toxicity of iodine is remarkably low in the concentrations used for water disinfection.[9,23-25] Only persons with a specific sensitivity to iodine, and perhaps those who have been treated for hyperthyroidism risk any ill effects. The only danger of the above procedure is the inadvertent ingestion of iodine crystals, although an ounce of iodine solution would be harmless. No fatality from ingestion of less than 15 grams of iodine has been reported.

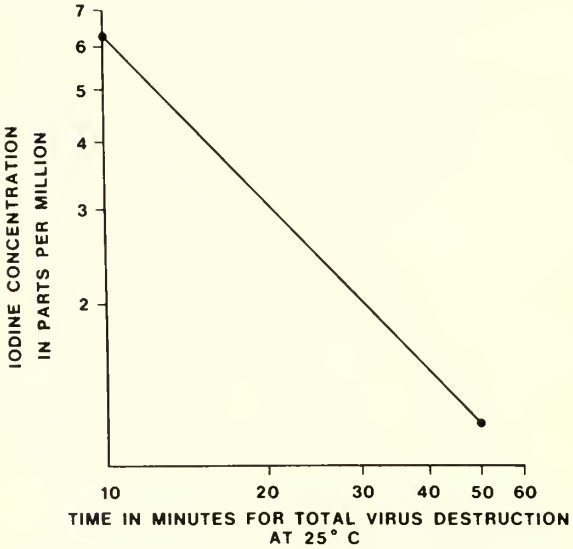

Chart 1.—The relationship of iodine concentration to contact time for the inactivation of enterovirus (Coxsackie B_1), taken from Chang.[5] This enterovirus has a high resistance to disinfection, estimated to be comparable to that of the infectious hepatitis virus.[8]

Conclusion

The use of iodine releasing tablets for emergency water disinfection has been employed by the United States Army since World War II, replacing chlorination with Halazone tablets. Chlorine,

TABLE 1.—*The Volume at Various Temperatures of a Near Saturated Solution of Iodine Added to One Liter of Water to Yield an Iodine Concentration of Four Parts per Million*

Temperature	*Volume*	*ppm*	*Capfuls**
3°C (37°F)	20.0 cc	200	8
20°C (68°F)	13.0 cc	300	5+
25°C (77°F)	12.5 cc	320	5
40°C (104°F)	10.0 cc	400	4

*Assuming a capful of standard 1 ounce glass bottle is 2½ cc.

except when breakpoint chlorination is practiced, is not a reliable disinfectant. This is so because the hydrolysis products of chlorine are less active at pH over 7 and in the presence of amino and ammonia ions. Iodination rapidly inactivates the known human pathogens, including the enteroviruses which are the most resistant to disinfection. Iodination is effective over a wide pH range, and in the presence of nitrogenous pollutants. A simple, lightweight iodination method using iodine crystals with unlimited shelf life is described for use by travelers and backpackers.

For a more detailed and technical discussion of water disinfection the reader is referred to the papers from the Sanitary Engineering Center, United States Public Health Service, Cincinnati, Ohio,[5,8,9,18] and the most current review of water disinfectants.[26]

Summary

There is a need among travelers and hikers for an effective, palatable water disinfectant with rapid action and long shelf life. A method of iodine disinfection which meets these requirements is described. A one ounce glass bottle containing 4 to 8 grams of iodine crystals is filled with water, then shaken vigorously to produce a near saturated solution of iodine. At 25°C (77°F), 12.5 cubic centimeters of this supernatant solution is added to one liter of water to be disinfected. In less than 15 minutes pathogenic bacteria, amebic cysts and viruses will be inactivated. This procedure can be repeated almost 1,000 times without replenishing the iodine crystals.

This method is compared with Halazone disinfection and other iodination methods, some of which are not currently available.

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in memoriam

ALLENDE, MANUEL FRANCISCO, San Francisco. Died March 26, 1975 in Norden, Nevada of myocardial infarction, aged 56. Graduate of Université de Paris Faculté de Médecine, 1942. Licensed in California in 1948. Dr. Allende was a member of the San Francisco Medical Society.

BACON, SAMUEL KENNETH, Hollywood. Died March 6, 1975 in Hollywood of myocardial infarction, aged 69. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1931. Licensed in California in 1931. Dr. Bacon was a member of the Los Angeles County Medical Association.

CHINNOCK, ROBERT F., Loma Linda. Died February 23, 1975 in Loma Linda, aged 55. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1944. Licensed in California in 1944. Dr. Chinnock was a member of the San Bernardino County Medical Society.

CUNNINGHAM, WILLIAM E., Richmond. Died March 17, 1975 in Richmond, aged 97. Graduate of Cooper Medical College, San Francisco, 1904. Licensed in California in 1904. Dr. Cunningham was a member of the Alameda-Contra Costa Medical Association.

DOYLE, JAMES C., Beverly Hills. Died March 10, 1975 in Palm Springs following a lung operation, aged 76. Graduate of Northwestern University Medical School, Chicago, 1928. Licensed in California in 1928. Dr. Doyle was a past president of the California Medical Association, a past Speaker of the California Medical Association's House of Delegates, and a member of the Los Angeles County Medical Association.

FAGAN, ROBERT H., Beverly Hills. Died February 11, 1975 in Riverside of myocardial infarction, aged 76. Graduate of the University of California Medical School, Berkeley-San Francisco, 1925. Licensed in California in 1925. Dr. Fagan was a retired member of the Los Angeles County Medical Association.

GOODMAN, DORIS RYAN, San Jose. Died March 18, 1975 of heart disease, aged 72. Graduate of Tufts University School of Medicine, Boston, 1934. Licensed in California in 1961. Dr. Goodman was a member of the Santa Clara County Medical Society.

LEBARON, GEORGE I., JR., Sacramento. Died March 17, 1975 in Oakland of injuries received in an automobile accident, aged 45. Graduate of the University of Rochester School of Medicine and Dentistry, 1955. Licensed in California in 1959. Dr. LeBaron was a member of the Sacramento Medical Association.

MANLEY, THOMAS MORGAN, La Jolla. Died September 29, 1974 in Yakima, Washington of emphysema and heart disease, aged 72. Graduate of the Creighton University School of Medicine, Omaha, 1927. Licensed in California in 1928. Dr. Manley was a retired member of the San Diego County Medical Society.

MCGAUGHEY, CLARK GRIFFITH, Newport Beach. Died February 16, 1975 of heart disease, aged 59. Graduate of the University of Michigan Medical School, Ann Arbor, 1943. Licensed in California in 1958. Dr. McGaughey was a member of the Orange County Medical Association.

MCIVOR, ROBERT JAMES, Oakland. Died March 6, 1975 in Oakland, aged 76. Graduate of University of California Medical School, Berkeley-San Francisco, 1931. Licensed in California in 1931. Dr. McIvor was a member of the Alameda-Contra Costa Medical Association.

NORMAN, JOHN G., San Pedro. Died February 27, 1975, aged 85. Graduate of the University of California Medical School, Berkeley-San Francisco, 1916. Licensed in California in 1916. Dr. Norman was a retired member of the Los Angeles County Medical Association.

RAINS, RICHARD RALPH, Brea. Died October 4, 1974 of myocardial infarction, aged 44. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1958. Licensed in California in 1959. M.D. degree from California College of Medicine, 1962. Dr. Rains was a member of the Forty First Medical Society.

SCHADE, FRANK FLORENCE, Los Angeles. Died March 19, 1975 in Los Angeles, aged 68. Graduate of the University of Pittsburgh School of Medicine, 1930. Licensed in California in 1936. Dr. Schade was a member of the Los Angeles County Medical Association.

STRUBLE, GILBERT C., Los Angeles. Died February 19, 1975, aged 68. Graduate of the University of Nebraska College of Medicine, Omaha, 1930. Licensed in California in 1946. Dr. Struble was a member of the Los Angeles County Medical Association.

TORRANO, MICHAEL ANGELO, Hayward. Died March 18, 1975 in Hayward, aged 83. Graduate of the University of California Medical School, Berkeley-San Francisco, 1922. Licensed in California in 1922. Dr. Torrano was a retired member of the Alameda-Contra Costa Medical Association.

VON BRIESEN, HANS, Los Angeles. Died February 27, 1975 in San Francisco, aged 74. Graduate of the University of California Medical School, Berkeley-San Francisco, 1928. Licensed in California in 1928. Dr. von Briesen was a retired member of the Los Angeles County Medical Association.

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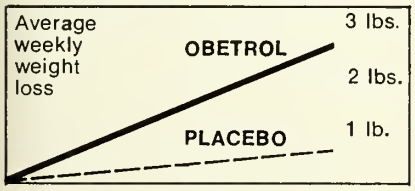

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Clinical studies disclose amphetamines to be the most dependable drug in a weight-reduction regimen compared to other anorexigenic agents.

Amphetamines have a significant potential for abuse. In view of their limited short-term anorectic effect and rapid development of tolerance, they should be used with extreme caution and only for limited periods of time in weight reduction programs.

Actions: Amphetamines are sympathomimetic amines with CNS stimulant activity. Peripheral actions include elevation of systolic and diastolic blood pressures and weak bronchodilator and respiratory stimulant action. The anorectic effect diminishes after a few weeks.

Indications: Exogenous obesity, as a short term (a few weeks) adjunct in a regimen of weight reduction based on caloric restriction. For patients in whom obesity is refractory to other measures.

Contraindications: Advanced arteriosclerosis, symptomatic cardiovascular disease, moderate to severe hypertension, hyperthyroidism, known hypersensitivity or idiosyncracy to the sympathomimetic amines. • Agitated states. • Patients with a history of drug abuse. • During or within 14 days following the administration of monoamine oxidase inhibitors, hypertensive crises may result.

Warnings: Tolerance to the anorectic effect usually develops within a few weeks. When this occurs, the recommended dose should not be exceeded in an attempt to increase the effect, rather, the drug should be discontinued. Amphetamines may impair the ability of the patient to engage in potentially hazardous activities such as operating machinery or driving a motor vehicle; the patient should therefore be cautioned accordingly.

Precautions: Caution is to be exercised in prescribing amphetamines for patients with even mild hypertension. Insulin requirements in diabetes mellitus may be altered in association with the use of amphetamines and the concomitant dietary regimen. Amphetamines may decrease the hypotensive effect of guanethidine. The least amount feasible should be prescribed or dispensed at one time in order to minimize the possibility of overdosage.

Adverse Reactions: *Cardiovascular:* Palpitation, tachycardia, elevation of blood pressure. Central nervous system: Overstimulation, restlessness, dizziness, insomnia, euphoria, dysphoria, tremor, headache; rarely, psychotic episodes at recommended doses. *Gastrointestinal:* Dryness of the mouth, unpleasant taste, diarrhea, other gastrointestinal disturbances. Anorexia and weight loss may occur as undesirable effects when amphetamines are used for other than the anorectic effect. *Allergic:* Urticaria. *Endocrine:* Impotence, changes in libido.

Dosage and Administration: Regardless of indication, amphetamines should be administered at the lowest effective dosage and dosage should be individually adjusted. Late evening medication should be avoided because of the resulting insomnia.

1. Narcolepsy: Usual dose 5 to 60 milligrams per day in divided doses.
2. Minimal brain dysfunction:
   a. Not recommended for children under 3 years of age.
   b. Children from 3 to 5 years of age: 2.5 milligrams daily, raised in increments of 2.5 milligrams at weekly intervals until optimal response is obtained.
   c. Children 6 years of age and older, 5 milligrams, once or twice daily, increased in increments of 5 milligrams at weekly intervals. Only in rare cases will it be necessary to exceed a total of 40 milligrams per day.
3. Obesity: Usual adult dose 5 to 30 milligrams per day in divided doses.

Overdosage: Manifestations of acute overdosage with amphetamines include restlessness, confusion, assaultiveness, hallucinations, panic states. Fatigue and depression usually follow the central stimulation. Cardiovascular effects include arrhythmias, hypertension or hypotension, and circulatory collapse. Gastrointestinal symptoms include nausea, vomiting, diarrhea, and abdominal cramps. Fatal poisoning usually terminates in convulsions and coma.

Management of acute amphetamine intoxication is largely symptomatic and includes lavage and sedation with a barbiturate. Experience with hemodialysis or peritoneal dialysis is inadequate to permit recommendations in this regard.

Availability: Supplied in bottles of 100; 500 and 1,000 tablets.

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January 1973

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vral® helps eliminate questions.

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*Serious as well as minor adverse reactions have been reported following the use of all oral contraceptives. The physician should remain alert to their earliest manifestations and in the event of serious adverse reactions should avoid any oral contraceptives. Special note, contraindications, warnings, precautions, and adverse reactions in the accompanying IN BRIEF should be carefully considered.

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Important information on next page.

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IN BRIEF.

SPECIAL NOTE: Oral contraceptives have been marketed in the United States since 1960. Reported pregnancy rates vary from product to product. The effectiveness of the sequential products appears to be somewhat lower than that of the combination products. Both types provide almost completely effective contraception.

An increased risk of thromboembolic disease associated with the use of hormonal contraceptives has now been shown in studies conducted in both Great Britain and the United States. Other risks, such as those of elevated blood pressure, liver disease and reduced tolerance to carbohydrates, have not been quantitated with precision.

Long-term administration of both natural and synthetic estrogens in subprimate animal species in multiples of the human dose increases the frequency for some animal carcinomas. These data cannot be transposed directly to man. The possible carcinogenicity due to the estrogens can neither be affirmed nor refuted at this time. Close clinical surveillance of all women taking oral contraceptives must be continued.

INDICATIONS: For oral contraception.

CONTRAINDICATIONS: 1. Thrombophlebitis, thromboembolic disorders, cerebral apoplexy, or a past history of these conditions. 2. Markedly impaired liver function; 3. Known or suspected carcinoma of the breast. 4. Known or suspected estrogen dependent neoplasia. 5. Undiagnosed abnormal genital bleeding.

WARNINGS: 1. The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism, and retinal thrombosis). Should any of these occur or be suspected, the drug should be discontinued immediately.

Retrospective studies of morbidity and mortality in Great Britain and studies of morbidity in the United States have shown a statistically significant association between thrombophlebitis, pulmonary embolism, and cerebral thrombosis and embolism and the use of oral contraceptives. There have been three principal studies in Britain[1-3] leading to this conclusion, and one[4] in this country. The estimate of the relative risk of thromboembolism in the study by Vessey and Doll[3] was about sevenfold, while Sartwell and associates in the United States found a relative risk of 4.4, meaning that the users are several times as likely to undergo thromboembolic disease without evident cause as non-users. The American study also indicated that the risk did not persist after discontinuation of administration and that it was not enhanced by long continued administration. The American study was not designed to evaluate a difference between products. However, the study suggested that there might be an increased risk of thromboembolic disease in users of sequential products. This risk cannot be quantitated, and further studies to confirm this finding are desirable.

(1) Royal College of General Practitioners: Oral Contraception and Thromboembolic Disease. J. Coll. Gen. Pract. 13:267-279, 1967. (2) Inman, W.H.W. and Vessey, M.P. Investigation of Deaths from Pulmonary Coronary and Cerebral Thrombosis and Embolism in Women in Child-Bearing Age. Brit. Med. J. 2:193-199, 1968. (3) Vessey, M.P. and Doll, R. Investigation of Relation between Use of Oral Contraceptives and Thromboembolic Disease. A Further Report. Brit. Med. J. 2:651-657, 1969. (4) Sartwell, P.E., Masi, A.T., Arthes, F.G., Greene, G.R., and Smith, H.E. Thromboembolism and Oral Contraceptives: An Epidemiological Case-Control Study. Am. J. Epidem. 90:365-380 (Nov.) 1969

2. Discontinue medication pending examination if there is sudden, partial or complete loss of vision, or if there is sudden onset of proptosis, diplopia, or migraine. If examination reveals papilledema or retinal vascular lesions, medication should be withdrawn. 3. Since the safety of Ovral in pregnancy has not been demonstrated, it is recommended that for any patient who has missed two consecutive periods, pregnancy should be ruled out before continuing the contraceptive regimen. If the patient has not adhered to prescribed schedule the possibility of pregnancy should be considered at the time of the first missed period. 4. A small fraction of the hormonal agents in oral contraceptives has been identified in the milk of mothers receiving these drugs. The long range effect to the nursing infant cannot be determined at this time.

PRECAUTIONS: 1. The pretreatment and periodic physical examinations should include special reference to breasts and pelvic organs, including Papanicolaou smear since estrogens have been known to produce tumors, some of them malignant, in five species of subprimate animals. 2. Endocrine and possibly liver-function tests may be affected by treatment with Ovral. Therefore, if such tests are abnormal in a patient taking Ovral, it is recommended that they be repeated after the drug has been withdrawn for two months. 3. Under the influence of estrogen-progestogen preparations, preexisting uterine fibromyomata may increase in size. 4. Because these agents may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, cardiac or renal dysfunction, require careful observation. 5. In breakthrough bleeding, and in all cases of irregular bleeding per vaginam, nonfunctional causes should be borne in mind. In undiagnosed bleeding per vaginam, adequate diagnostic measures are indicated. 6. Patients with a history of psychic depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree. 7. Any possible influence of prolonged Ovral therapy on pituitary, ovarian, adrenal, hepatic or uterine function awaits further study. 8. A decrease in glucose tolerance has been observed in a significant percentage of patients on oral contraceptives. The mechanism of this decrease is obscure. For this reason, diabetic patients should be carefully observed while receiving Ovral therapy. 9. The age of the patient constitutes no absolute limiting factor, although treatment with Ovral may mask the onset of the climacteric. 10. The pathologist should be advised of Ovral therapy when relevant specimens are submitted. 11. Susceptible women may experience an increase in blood pressure following administration of contraceptive steroids.

ADVERSE REACTIONS OBSERVED IN PATIENTS RECEIVING ORAL CONTRACEPTIVES: A statistically significant association has been demonstrated between use of oral contraceptives and the following serious adverse reactions: thrombophlebitis, pulmonary embolism, cerebral thrombosis.

Although available evidence is suggestive of an association, such a relationship has been neither confirmed nor refuted for the following serious adverse reactions: neuro-ocular lesions (e.g., retinal thrombosis and optic neuritis).

The following adverse reactions are known to occur in patients receiving oral contraceptives: nausea, vomiting, gastrointestinal symptoms (e.g., abdominal cramps and bloating), breakthrough bleeding, spotting, change in menstrual flow, amenorrhea during and after treatment, dysmenorrhea, edema, chloasma or melasma, breast changes (tenderness, discomfort, enlargement and secretion), change in weight (increase or decrease), changes in cervical erosion and cervical secretions, suppression of lactation when given immediately post-partum, cholestatic jaundice, migraine, acne, rash (allergic), hypertension, rise in blood pressure in susceptible individuals, mental depression, pain in legs, arms or body, paresthesias, allergy, palpitations, vasomotor symptoms, dyspnea, insomnia, blurred vision, chest pain, urinary tract symptoms, dyspareunia, neuralgia and myalgia, excess salivation, dryness of mouth, heartburn, minor eye problems.

Although the following adverse reactions have been reported in users of oral contraceptives, an association has been neither confirmed nor refuted: anovulation post-treatment, premenstrual-like syndrome, changes in libido, changes in appetite, cystitis-like syndrome, headache, nervousness, dizziness, fatigue, backache, hirsutism, loss of scalp hair, erythema multiforme, erythema nodosum, hemorrhagic eruption, and itching and vaginal discharge.

The following laboratory results may be altered by the use of oral contraceptives—hepatic function: increased sulfobromophthalein retention and other tests; coagulation tests: increase in prothrombin, Factors VII, VIII, IX and X; thyroid function: increase in PBI and butanol-extractable protein-bound iodine and decrease in T_3 uptake values; metyrapone test; and pregnanediol determination.

Note: For more specific details on Ovral, refer to package insert.

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COMMITTEE ON CONTINUING MEDICAL EDUCATION

THIS BULLETIN of information regarding continuing education programs and meetings of various medical organizations in **California and Hawaii** is supplied by the Committee on Continuing Medical Education of the California Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Committee on Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103; or phone (415) 777-2000. Note: Please see **California Medicine,** Vol. 117, No. 4, October, 1972 issue for a list of organizations approved for Category I Credit toward the CMA Certificate in Continuing Medical Education.

CANCER

May 28-30—**Cancer. USC.** Wednesday-Friday.

August 21-22—**Multidisciplinary Approach to Cancer Treatment.** UCSF at Children's Hospital, San Francisco. Thursday-Friday.

MEDICINE

May 15-16—**American Heart Association, California Affiliate.** Del Monte Hyatt House, Monterey. Thursday-Friday. Contact: Marilyn Probst, Admin. Asst., AHA, Calif. Affiliate, 1370 Mission St., San Francisco 94103. (415) 626-0123.

May 19-23.—**Advances in Internal Medicine.** UCSF. Monday-Friday.

May 29-31—**Ischemic Heart Disease: A Critical Overview.** PMC and American College of Cardiology at Golden Gateway Holiday Inn, San Francisco. Thursday-Saturday.

May 31—**Head and Spinal Cord Injuries.** See Surgery, May 31.

June 4-7—**Core Curriculum in Echocardiography: New Developments in Cardiac Ultrasound.** American College of Cardiology at Town and Country Hotel, San Diego. Wednesday-Saturday. Contact: Mary Anne McInerny, Dir., Dept. of Cont. Ed. Programs, 9650 Rockville Pike, Bethesda, Md., 20014. (301) 530-1600.

June 13—**The Inaugural Warden Lecture Series: Current Topics in Thoracic Disease.** Naval Regional Medical Center, San Diego. Friday. Contact: Capt. R. G. Fosburg, MC, USN, Box 255, NRMC, San Diego 92134. (714) 233-2365.

June 14—**Allergy for the Busy Office Practice.** PMC. Saturday. 6 hrs. $75.

July 21-24—**Primary Care Dermatology.** STAN. Monday-Thursday.

August 13-17—**Advanced Seminar in Dermatology.** UCI at Newporter Inn, Newport Beach. Wednesday-Sunday.

OBSTETRICS AND GYNECOLOGY

May 16-17—**Obstetrics and Gynecology Symposium.** Southern Calif. Permanente Medical Group at Sheraton Hotel, Anaheim. Friday-Saturday. Contact: Shirley Gach, So. Calif. Permanente Medical Group, 4900 Sunset Blvd., Los Angeles 90027. (213) 667-4242.

May 16-17—**Academic and Practical Application of Laparoscopy.** UCLA. Friday-Saturday.

May 19-22—**Ob/Endocrinology and Infertility.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. Monday-Thursday.

June 13—**Prematurity Conference.** See Pediatrics, June 13.

PEDIATRICS

May 16-18—**American Academy of Pediatrics, Northern California Chapter.** Ahwahnee Hotel, Yosemite. Friday-Sunday. Contact: Melvin Schwartz, MD, 2219 Santa Clara Ave., Alameda 94501. (415) 523-3417.

May 17-18—**Hypertension in Children and Adolescents: Facts, Fictions and Controversies.** Memorial Hosp. Med. Ctr. of Long Beach, Children's Hosp. of Long Beach, Children's Hosp. of Los Angeles at Center for Health Education, Long Beach. Saturday-Sunday. Contact: Executive Secretary, Center for Health Education, 2801 Atlantic Ave., Long Beach 90801.

May 18-21—**Heart and Lung Disease in Neonates and Infants.** UCLA at Ahwahnee Hotel, Yosemite. Sunday-Wednesday.

May 22-23—**Sensory and Perceptual Dysfunctioning in Early Childhood: Some Approaches to Therapy.** See Surgery, May 22-23.

May 31-June 1—**Attentional Disorders in Children.** UCLA at Asilomar Conference Grounds, Monterey. Saturday-Sunday.

KEY TO ABBREVIATIONS AND SYMBOLS

Medical Centers and CMA Contacts for Information

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103. (415) 777-2000.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Duane Dillman, PhD, Director, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 564-5911, ext. 391.

LLU: Loma Linda University
Contact: John E. Peterson, MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311.

PMC: Pacific Medical Center
Contact: Allen J. Enelow, MD, Chairman, Education Committee, Pacific Medical Center, P.O. Box 7999, San Francisco 94120. (415) 563-4321.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Neil C. Andrews, MD, Chairman, Department of Postgraduate Medicine, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, California College of Medicine, Irvine
Contact: Robert Combs, MD, Associate Dean, Continuing Medical Education, University of California, Irvine—California College of Medicine, Irvine 92664. (714) 833-5991.

UCLA: University of California, Los Angeles
Contact: Donald Brayton, MD, Director Continuing Education in Medicine and the Health Sciences. P.O. Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: Richard A. Lockwood, MD, Associate Dean for Health Manpower, 1310 Basic Sciences Building, University of California, San Diego, School of Medicine, La Jolla 92037. (714) 453-2000, ext. 1251.

UCSF: University of California, San Francisco
Contact: Malcolm S. M. Watts, MD, Associate Dean and Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-2342.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 226-2047.

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June 13—**Prematurity Conference—14th Annual.** STAN. Friday.

June 24-28—**National Society for Autistic Children.** See Psychiatry, June 24-28.

July 1-3—**Thirty Grams of Prevention—Annual Pediatric Seminar.** Children's Hospital and Health Center, San Diego, at Hotel del Coronado, Coronado. Tuesday-Thursday. 16 hrs. $30. Contact: Mrs. Franci Perkins, Sec. to Med. Dir., Children's Hospital and Health Center, 8001 Frost St., San Diego 92123. (714) 277-5808, ext. 351.

PSYCHIATRY

May 21-26—**Psychiatric Update—2nd Annual.** UCLA at Ahwahnee Hotel, Yosemite. Wednesday-Monday.

May 31-June 1—**Attentional Disorders in Children.** See Pediatrics, May 31-June 1.

June 1-4—**Biofeedback.** UCLA at Asilomar Conference Grounds, Pacific Grove. Sunday-Wednesday.

June 14—**Individual Dangerousness: What Do We Know About Prediction and Management?** UCLA. Saturday.

June 23-27—**Comparative Psychotherapies.** USC at The Waystation, Lake Tahoe. Monday-Friday. 21 hrs. $150. Contact: Donald H. Naftulin, MD, Dir., Cont. Ed. in Psych., USC. (213) 226-2114.

June 24-28—**National Society for Autistic Children—Annual Meeting.** Town and Country Hotel, San Diego. Thursday-Saturday. $30-45. Contact: Alma Spicer, 1437 Torrence St., San Diego 92103. (714) 299-3808.

July 26-27—**A Biofeedback Workshop.** UC, Santa Cruz. Saturday-Sunday. 15 hrs. $75. Contact: Darla Chadima, Cont. Ed. Specialist, Applied Sciences Bldg., UC Extension, Santa Cruz 95064. (408) 429-2971.

RADIOLOGY AND PATHOLOGY

June 4-7—**Core Curriculum in Echocardiography: New Developments in Cardiac Ultrasound.** See Medicine, June 4-7.

June 4-7—**California Radiological Society—Annual Scientific Meeting.** Hotel del Coronado, Coronado. Wednesday-Saturday. Contact: CRS, 1225 8th St., Suite 590, Sacramento 95814.

SURGERY AND ANESTHESIOLOGY

May 15-17—**Neurosurgery.** UCSF and American College of Surgeons at Hilton Hotel, San Francisco. Thursday-Saturday.

May 17—**American College of Surgeons, Northern California Chapter.** Hilton Hotel, San Francisco. Saturday. Contact: Dorothy Archbold, Exec. Sec., 2249 Van Ness Ave., No. 2, San Francisco 94109. (415) 221-4810, ext. 251

May 17—**Surgical Anatomy and Surgery of the Chest.** International College of Surgeons, U.S. Section, at Los Angeles Orthopaedic Hospital. Saturday. 8 hrs. $50. Contact: Irving Rehman, PhD, Chr., Postgraduate and Ongoing Education Committee, 5153 Tampa Ave., Tarzana 91356. (213) 344-3305.

May 22-23—**Phaco-Fragmentation.** UCSF. Thursday-Friday.

May 22-23—**Sensory and Perceptual Dysfunctioning in Early Childhood: Some Approaches to Therapy.** USC. Thursday-Friday.

May 25-29—**American College of Emergency Physicians, California Chapter.** See Of Interest To All, May 25-29.

May 31—**Head and Spinal Cord Injuries.** DREW at Martin Luther King Hospital, Los Angeles. Saturday.

June 6-7—**Tendon and Nerve Injuries of the Hand.** PMC. Friday-Saturday.

June 7—**Phacoemulsification with Insertion of an Intraocular Lens.** St. Mary's Hospital and Medical Center, San Francisco. Saturday. $200. Contact: St. Mary's Hospital and Medical Center, 2200 Hayes St., San Francisco 94117.

June 12-13—**Highlights of Modern Ophthalmology.** PMC at Golden Gateway Holiday Inn, San Francisco. Thursday-Friday.

June 12-15—**California Society of Anesthesiologists—Annual Scientific Meeting.** Hyatt Regency, San Francisco. Thursday-Sunday. Contact: Norman Catron, Exec. Sec., CSA, 100 S. Ellsworth Ave., Suite 806, San Mateo 94401. (415) 343-4644.

June 13—**The Inaugural Warden Lecture Series: Current Topics in Thoracic Disease.** See Medicine, June 13.

June 13-14—**Trauma.** UCSF at Mary's Help Hospital, San Francisco. Friday-Saturday.

June 19-20—**Practical Management of External and Corneal Disease Problems.** USC. Thursday-Friday.

June 26-27—**Phaco-Fragmentation.** UCSF. Thursday-Friday.

June 28-30—**Phacoemulsification.** St. Mary's Hospital and Medical Center, San Francisco. Saturday-Monday. $600. Contact: St. Mary's Hospital and Medical Center, 2200 Hayes St., San Francisco 94117.

July 17-18—**Phaco-Fragmentation.** UCSF. Thursday-Friday.

July 19—**Phacoemulsification with Insertion of an Intraocular Lens.** St. Mary's Hospital and Medical Center, San Francisco. Saturday. $200. Contact: St. Mary's Hospital and Medical Center, 2200 Hayes St., San Francisco 94117.

August 6-10—**Urology—Annual Advanced Seminar.** UCLA at UC Residential Conference Center, Lake Arrowhead. Wednesday-Sunday.

August 7-8—**Phaco-Fragmentation.** UCSF. Thursday-Friday.

August 17-29—**Temporal Bone Surgical Dissection Course.** Ear Research Institute, Los Angeles. Two weeks. $1200 for otolaryngologists; $900 for residents. Contact: Jack L. Pulec, MD, Ear Research Institute, 2130 W. 3rd St., Los Angeles 90057.

(Continued on Page 39)

How many of your patients know what the B vitamins are?

But they do know what breads and cereals are.

The foods above have several nutrients in common. Among them are the vitamin B complex, necessary for healthy skin and a well-functioning nervous system. The B vitamins include thiamin (B_1), niacin and riboflavin (B_2). These foods are classified as the Bread & Cereal Group in the U.S. Department of Agriculture's Four Food Groups system.

Some physicians counsel patients in terms of nutrients. Which is easier for them to understand—foods or nutrients?

For attractive, color copies of the Four Food Groups guide for your patients, write: Dairy Council of California, Box 28F, Sacramento, CA 95825.

Dairy Council of California

The Four Food Groups—milk, meat, vegetables and fruits, breads and cereals—a practical guide to good nutrition.

THE NATURAL WAY

For more than thirty years PREMARIN (Conjugated Estrogens Tablets, U.S.P.) has been prepared with natural equine estrogens exclusively—without synthetic estrogen supplements. For more than thirty years it has provided the complete estrogen complex in the proportions found in its natural source. And for more than thirty years PREMARIN has enjoyed an unparalleled record of clinical efficacy and acceptance.

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Indications: Based on a review of PREMARIN Tablets by the National Academy of Sciences-National Research Council and/or other information, FDA has classified the indications for use as follows:
Effective: As replacement therapy for naturally occurring or surgically induced estrogen deficiency states associated with: the climacteric, including the menopausal syndrome and postmenopause; senile vaginitis and kraurosis vulvae, with or without pruritus.
"Probably" effective: For estrogen deficiency-induced osteoporosis, and only when used in conjunction with other important therapeutic measures such as diet, calcium, physiotherapy, and good general health-promoting measures. Final classification of this indication requires further investigation.

Contraindications: Short acting estrogens are contraindicated in patients with (1) markedly impaired liver function; (2) known or suspected carcinoma of the breast, except those cases of progressing disease not amenable to surgery or irradiation occurring in women who are at least 5 years postmenopausal; (3) known or suspected estrogen-dependent neoplasia, such as carcinoma of the endometrium; (4) thromboembolic disorders, thrombophlebitis, cerebral embolism, or in patients with a past history of these conditions; (5) undiagnosed abnormal genital bleeding.
Warnings: Estrogen therapy should not be given to women with recurrent chronic mastitis or abnormal mammograms except, if in the opinion of the physician, it is warranted despite the possibility of aggravation of the mastitis or stimulation of undiagnosed estrogen-dependent neoplasia.

The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, retinal thrombosis, cerebral embolism and pulmonary embolism). If these occur or are suspected, estrogen therapy should be discontinued immediately.

Estrogens may be excreted in the mother's milk and an estrogenic effect upon the infant has been described. The long range effect on the nursing infant cannot be determined at this time.

Hypercalcemia may occur in as many as 15 percent of breast cancer patients with metastases, and this usually indicates progression of bone metastases. This occurrence depends neither on dose nor on immobilization. In the presence of progression of the cancer or hypercalcemia, estrogen administration should be stopped.

A statistically significant association has been reported between maternal ingestion of diethylstilbestrol during pregnancy and the occurrence of vaginal carcinoma in the offspring. This occurred with the use of diethylstilbestrol for the treatment of threatened abortion or high risk pregnancies. Whether or not such an association is applicable to all estrogens is not known at this time. In view of this finding, however, the use of any estrogen in pregnancy is not recommended.

Failure to control abnormal uterine bleeding or unexpected recurrence is an indication for curettage.
Precautions: As with all short acting estrogens, the following precautions should be observed:

A complete pretreatment physical examination should be performed with special reference to pelvic and breast examinations.

To avoid prolonged stimulation of the endometrium and breasts in climacteric or hypogonadal women, estrogens should be administered cyclically (3 week regimen with 1 week rest period—withdrawal bleeding may occur during rest period).

Because of individual variation in endogenous estrogen production, relative overdosage may occur which could cause undesirable effects such as abnormal or excessive uterine bleeding, mastodynia and edema.

Because of salt and water retention associated with estrogenic anabolic activity, estrogens should be used with caution in patients with epilepsy, migraine, asthma, cardiac, or renal disease.

If unexplained or excessive vaginal bleeding should occur, reexamination should be made for organic pathology.

Pre-existing uterine fibromyomata may increase in size while using estrogens; therefore, patients should be examined at regular intervals while receiving estrogenic therapy.

The pathologist should be advised of estrogen therapy when relevant specimens are submitted.

Because of their effects on epiphyseal closure, estrogens should be used judiciously in young patients in whom bone growth is incomplete.

Prolonged high dosages of estrogens will inhibit anterior pituitary functions. This should be borne in mind when treating patients in whom fertility is desired.

The age of the patient constitutes no absolute limiting factor, although treatment with estrogens may mask the onset of the climacteric.

Certain liver and endocrine function tests may be affected by exogenous estrogen administration. If test results are abnormal in a patient taking estrogen, they should be repeated after estrogen has been withdrawn for one cycle.
Adverse Reactions: The following adverse reactions have been reported associated with short acting estrogen administration:
nausea, vomiting, anorexia
gastrointestinal symptoms such as abdominal cramps and bloating
breakthrough bleeding, spotting, unusually heavy withdrawal bleeding (See DOSAGE AND ADMINISTRATION)
breast tenderness and enlargement
reactivation of endometriosis
possible diminution of lactation when given immediately postpartum
loss of libido and gynecomastia in males
edema
aggravation of migraine headaches
change in body weight (increase, decrease)
headache
allergic rash
hepatic cutaneous porphyria becoming manifest
Dosage and Administration: PREMARIN should be administered cyclically (3 weeks of daily estrogen and 1 week off) for all indications except selected cases of carcinoma and prevention of postpartum breast engorgement.

Menopausal Syndrome—1.25 mg. daily, cyclically. Adjust dosage upward or downward according to severity of symptoms and response of the patient. For maintenance, adjust dosage to lowest level that will provide effective control.

If the patient has not menstruated within the last two months or more, cyclic administration is started arbitrarily. If the patient is menstruating, cyclic administration is started on day 5 of bleeding. If breakthrough bleeding (bleeding or spotting during estrogen therapy) occurs, increase estrogen dosage as needed to stop bleeding. In the following cycle, employ the dosage level used to stop breakthrough bleeding in the previous cycle. In subsequent cycles, the estrogen dosage is gradually reduced to the lowest level which will maintain the patient symptom-free.

Postmenopause—as a protective measure against estrogen deficiency-induced degenerative changes (*e.g.* osteoporosis, atrophic vaginitis, kraurosis vulvae)—0.3 mg. to 1.25 mg. daily and cyclically. Adjust dosage to lowest effective level.

Osteoporosis (to retard progression)—usual dosage 1.25 mg. daily and cyclically.

Senile Vaginitis, Kraurosis Vulvae with or without Pruritus—0.3 mg. to 1.25 mg. or more daily, depending upon the tissue response of the individual patient. Administer cyclically.
How Supplied: PREMARIN (Conjugated Estrogens Tablets, U.S.P.)

No. 865—Each *purple* tablet contains 2.5 mg., in bottles of 100 and 1,000.

No. 866—Each *yellow* tablet contains 1.25 mg., in bottles of 100 and 1,000. Also in unit dose package of 100.

No. 867—Each *red* tablet contains 0.625 mg., in bottles of 100 and 1,000.

No. 868—Each *green* tablet contains 0.3 mg., in bottles of 100 and 1,000. 7352

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"Antiacid" action for ulcer patients...

one of the many things you need in an anticholinergic.

Pro-Banthīne is considered adjunctive in total peptic ulcer therapy that may include diet, conventional antacids, bed rest, and other supportive measu

Pro-Banthīne is provided in several different dosage forms which will me virtually any clinical need. It is just as versatile in filling patient needs, amo which are:

"Antiacid" action—Pro-Banthīne® (propantheline bromide) reduces ga secretory volume and resting total an free acid.

"Analgesic" action—Pro-Banthīne he to control the acid-spasm-pain comple

Vigorous anticholinergic action—Pro-Banthīne® Vials, 30 mg., are for intramuscular or intravenous use whe prompt and vigorous anticholinergic action is required.

Mild anticholinergic action—Pro-Banthīne® Half Strength, 7.5 mg. tablets, for more exact adjustment of maintenance dosage in mild to moderate gastrointestinal disorders.

Pro-Banthīn
(propantheline bromide)

a good option in peptic ulcer

Pro-Banthīne®
brand of
propantheline bromide

Indications: Pro-Banthīne is effective as adjunctive therapy in the treatment of peptic ulcer. Dosage must be adjusted to the individual.

Contraindications: Glaucoma, obstructive disease of the gastrointestinal tract, obstructive uropathy, intestinal atony, toxic megacolon, hiatal hernia associated with reflux esophagitis, or unstable cardiovascular adjustment in acute hemorrhage.

Warnings: Patients with severe cardiac disease should be given this medication with caution. Fever and possibly heat stroke may occur due to anhidrosis.

Overdosage may cause a curare-like action, with loss of voluntary muscle control. For such patients prompt and continuing artificial respiration should be applied until the drug effect has been exhausted. Diarrhea in an ileostomy patient may indicate obstruction, and this possibility should be considered before administering Pro-Banthīne.

Precautions: Since varying degrees of urinary hesitancy may be evidenced by elderly males with prostatic hypertrophy, such patients should be advised to micturate at the time of taking the medication.

Overdosage should be avoided in patients severely ill with ulcerative colitis.

Adverse Reactions: Varying degrees of drying of salivary secretions may occur as well as mydriasis and blurred vision. In addition the following adverse reactions have been reported: nervousness, drowsiness, dizziness, insomnia, headache, loss of the sense of taste, nausea, vomiting, constipation, impotence and allergic dermatitis.

Dosage and Administration: The recommended daily dosage for adult oral therapy is one 15-mg. tablet with meals and two at bedtime. Subsequent adjustment to the patient's requirements and tolerance must be made.

How Supplied: Pro-Banthīne is supplied as tablets of 15 and 7.5 mg., as prolonged-acting tablets of 30 mg. and, for parenteral use, as serum-type vials of 30 mg.

SEARLE **Searle & Co.**
San Juan, Puerto Rico 00936

Address medical inquiries to: G. D. Searle & Co. Medical Department, Box 5110, Chicago, Ill. 60680 481

(Continued from Page 34)

OF INTEREST TO ALL PHYSICIANS

May 17—**Clinical Pharmacology Conference — 6th Annual.** STAN at Palo Alto Medical Research Foundation, Palo Alto. Saturday.

May 19-23—**Topics in Emergency Medicine.** UCSF. Monday-Friday.

May 21—**Medical Education at the Crossroads—XVII Annual Medical Staff Symposium.** Memorial Hospital Medical Center, Long Beach. Wednesday. Contact: Margaret Frederick, Exec. Sec., Center for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3823.

May 25-29—**American College of Emergency Physicians, California Chapter—4th Annual Scientific Assembly.** Sheraton-Harbor Island Hotel, San Diego. Sunday-Thursday. 14 hrs. $100, ACEP members registering before April 30; $125, members registering after April 30 and non-members. Contact: ACEP, Calif. Chapter, 23 Altarinda Rd., Suite C, Orinda 94563.

June 4-6—**UCLA School of Medicine Alumni Postgraduate Institute.** Wednesday-Friday.

June 19-21—**Management of Medical Problems for the Family Physician.** PMC at Miyako Hotel, San Francisco. Thursday-Saturday.

June 22-25—**The Physician as Sex Educator and Counselor.** UCLA at Asilomar Conference Grounds, Pacific Grove. Sunday-Wednesday.

August 11-15—**Postgraduate Refresher Course—18th Annual.** USC at Sheraton-Waikiki Hotel, Honolulu. Monday-Friday.

August 20-24—**Family Practice Refresher Course—2nd Annual.** UCLA and Santa Monica Medical Center. Wednesday-Sunday.

August 24-29—**Family Practice Refresher Course—3rd Annual.** UCD. Sunday-Friday.

PRECEPTORSHIPS AND TRAINEESHIPS

Training for Physicians in General Internal Medicine. LLU. Four weeks or more, by arrangement. Bedside and classroom training, practical aspects of clinical care and management. 160 hrs. Contact: John E. Peterson, MD, LLU.

Training of Physicians in Modern Concepts of Pulmonary Care. LLU. Four weeks or more, by arrangement. Diagnostic and therapeutic methods in medical chest disease, physiological methodology of modern pulmonary care programs, use of new instrumentation in the field. 160 hrs. Contact: John E. Hodgkin, MD, Chief, Section of Medical Chest Diseases, LLU.

Training for Physicians in Nephrology. LLU. Four weeks or more, by arrangement. Hemodialysis, peritoneal displays, renal biopsy, and kidney transplantation. 160 hrs. Contact: Robert E. Soderblom, MD, LLU.

Preceptorships in Cardiology. PMC. By arrangement. $200 per mo.; $500 for 3 mos. Contact: Arthur Selzer, MD, PMC.

Preceptorships in Practical Office Dermatology. PMC. Wednesdays or Fridays, 9:00 a.m.-12:00 noon, for 10 weeks. Periods begin Oct., Jan., or April. $100. Contact: Harold M. Schneidman, MD, Dept. of Dermatology, PMC.

Preceptorships in Infectious Disease. PMC. Full time for four weeks. To be arranged. $250. Contact: Rodney J. Valentine, MD, Chief, Div. of Infectious Diseases, PMC.

Preceptorships in Basic Sciences, Biochemistry and Biophysics, Dermatology, Echocardiography, International Health, Microbiology, Neurological Surgery, Obstetrics and Gynecology, Pediatrics, Pharmacology and Experimental Therapeutics, Physiology, Psychiatry, Urology. UCSF. By special arrangement.

Traineeships in Renal Dialysis. UCSF. By special arrangement.

(Continued on Page 41)

When low back pain* interferes...

Help relieve pain, restore mobility with

PARAFON FORTE® tablets

chlorzoxazone 250 mg, acetaminophen 300 mg

*This drug has been evaluated as "probably" effective for this indication.

See brief summary of prescribing information on facing page for Indications, Contraindications, Warnings, Precautions and Adverse Reactions.

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PARAFON FORTE® tablets help relieve pain, restore mobility and stop pain-spasm feedback by providing:

a nonsalicylate analgesic equal to aspirin for relief of pain,[1,2] yet unlikely to cause the gastric irritation,[2,3] allergic reactions[2] or increased bleeding time[4] associated with aspirin therapy...

and a skeletal muscle relaxant shown in extensive clinical studies to afford relief of discomfort in acute musculoskeletal conditions*[5-7] but which is not an antihistamine or tranquilizer derivative and is unlikely to produce a tranquilizing or sedative effect.[5,7,8]

Indications: Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:

"Probably" effective as an adjunct to rest and physical therapy for the relief of discomfort associated with acute, painful musculoskeletal conditions. The mode of action of this drug has not been clearly identified, but may be related to its sedative properties. Chlorzoxazone does not directly relax tense skeletal muscles in man.

ntraindications: Sensitivity to either component.

rnings: *Usage in Pregnancy*—Use in women of childbearing ential only when potential benefits outweigh possible risks.

cautions: Exercise caution in patients with known allergies or ory of drug allergies. If a sensitivity reaction or any signs or symp- ns suggestive of liver dysfunction are observed, the drug should stopped.

verse Reactions: Occasionally, drowsiness, dizziness, lightheadess, malaise, overstimulation or gastrointestinal disturbances be noted; rarely, allergic-type skin rashes, petechiae, ecchyses, angioneurotic edema or anaphylactic reactions. In rare inces, chlorzoxazone may possibly have been associated with rointestinal bleeding. While PARAFLEX® (chlorzoxazone) tab- and other chlorzoxazone-containing products have been sused as being the cause of hepatic toxicity in approximately nty-four patients, it was not possible to state that the dysfunction or was not drug induced.

al Adult Dosage: Two tablets q.i.d.

plied: Scored, light green tablets, imprinted "McNEIL"—bottles 00.

rences: 1. Batterman, R.C., and Grossman, A.J.: Fed. Proc. *14*:316, 2. Goodman, L.S., and Gilman, A., ed.: The Pharmacological Basis of apeutics, ed. 4. New York, The Macmillan Company, 1970. 3. Vickers, Gastroint. Endosc. *14*:94, 1967. 4. Mielke, C.H., Jr., and Britten, A.F.H.: Engl. J. Med. *282*:1270, 1970 (Corresp.). 5. Vernon, W.G.: Curr. Therap. *14*:801, 1972. 6. Scheiner, J.J.: Curr. Therap. Res. *14*:168, 1972. 7. er, J.M.: Curr. Therap. Res. *15*:248, 1973. 8. Data on file, McNeil Labora-, Inc.

† U.S. Patent No. 2,895,877

McNEIL McNeil Laboratories, Inc.
Fort Washington, Pa. 19034

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OREGON

COUNCIL ON MEDICAL EDUCATION

THIS BULLETIN of information regarding continuing education programs and meetings of various medical organizations in Oregon is supplied by the Council on Medical Education of the Oregon Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Council on Medical Education, Oregon Medical Association, 2164 S.W. Park Place, Portland, Oregon 97205; or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

University of Oregon Medical School, Family Practice Center, 3181 S.W. Sam Jackson Park Road, Portland 97201:

Every Thursday, 8:00 a.m. to 9:00 a.m.—**Family Practice Grand Rounds.** Contact: David D. Smith, MD, Department of Family Practice, University of Oregon Medical School.

Providence Hospital, 700 N.E. 47th Ave., Portland 97213 (Contact: Marian Campbell, Department of Medical Education, 503-234-8211):

May 21, Wednesday, 8:00 a.m. (Auditorium, Providence Hall) —**Modern Concepts and Treatment of Severe Hypertension**—W. Bennett, MD.

May 28, Wednesday, 8:00 a.m. (Auditorium, Providence Hall) —**Results of the Analysis of Ileo-jejunal Bypass Surgery at Providence Hospital**—R. Gore, MD.

ANESTHESIOLOGY

May 17-19—**Oregon Society of Anesthesiologists, Inc. Annual Meeting.** Salishan, Gleneden Beach, Oregon 97388. Contact: Lynn Husband, MD, 2212 N.W. Pettygrove, Portland 97210.

CARDIOLOGY

June 5-7—**Progress in Coronary Artery Disease and Valvular Heart Disease.** Portland. Contact: S. H. Rahimtoola, University of Oregon Medical School, 3181 S.W. Sam Jackson Park Road, Portland 97201.

FAMILY PRACTICE

Every Thursday, 8:00 a.m. to 9:00 a.m.—**Family Practice Grand Rounds.** Family Practice Center, University of Oregon Medical School, Portland. Contact: David D. Smith, MD, Department of Family Practice, University of Oregon Medical School, 3181 S.W. Sam Jackson Park Road, Portland 97201.

INTERNAL MEDICINE

May 15-17—**Oregon Society of Internal Medicine Annual Meeting.** Inn of the Sevnth Mountain, Bend. Contact: Ted Lawson, Oregon Society of Internal Medicine, 2164 S.W. Park Place, Portland 97205.

NEUROLOGY

June 7-8—**Oregon Neurosurgical Society Annual Meeting.** Jantzen Beach Thunderbird, Portland. Contact: Michael Mason, MD, 2525 N.W. Lovejoy, Portland 97210.

OF INTEREST TO ALL PHYSICIANS

May 18-23—**Action and Accountability for Mental Development.** Portland Hilton, Portland. Contact: The American

Association on Mental Deficiency, 5201 Connecticut Avenue, N.W., Washington, D.C. 20015 (202) 244-8143.

May 23-26—**Physicians Institute Meeting.** Inn of the Seventh Mountain, Bend. Contact: Richard O'Shea, MD, 440 A Avenue, Lake Oswego 97034.

May 30-31—**Hypertension: The Challenge to the Clinician.** Portland, Jantzen Beach Thunderbird. Sponsored by the University of Oregon Medical School. Contact: M. Roberts Grover, Jr., MD, Associate Dean, University of Oregon Medical School, 3181 SW Sam Jackson Park Road, Portland 97201, (503) 225-8228. Acceptable for 10 hours Category I credit.

WASHINGTON, MONTANA, ALASKA and IDAHO

In order to have future activities listed here or to receive information on these and other activities, please write Ms. Joan M. Kelday, Information Specialist, Continuing Medical Education, WAMI Program, University of Washington School of Medicine, E-301, Health Sciences Building, SC-45, Seattle, Washington 98195. Phone: (206) 543-6995.

May 12-16—**Trauma-Burns-Shock: Emergency Medical Care—Univ. of Washington School of Medicine's Montana Circuit Course.** Great Falls, May 12; Billings, May 13; Bozeman, May 14; Missoula, May 15; Kalispell, May 16. 4 hrs. $25. Contact: Richard L. Reimer, Asst. Dir. CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

May 14-16—**Advances in Internal Medicine.** Wednesday-Friday. University Tower Hotel, Seattle. 18 hrs. $150. Contact: Richard L. Reimer, Asst. Dir. CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

May 16-17—**Washington Academy of Family Physicians Annual Meeting.** Friday-Saturday. Inn-at-the-Quay, Vancouver, Wash. 10 AAFP hrs. Contact: Walter Lapsley, Exec. Secretary, WAFP, 10003 SE Evergreen Highway, Vancouver, WA 98664.

May 16-17—**Puget Sound Academy of Otolaryngology Annual Meeting.** Friday-Saturday. Olympic Hotel, Seattle. Contact: Joseph W. Walike, MD, 1118 9th Ave., Seattle 98101. (206) 623-3700.

May 22-23—**Pediatric Care for Family Practitioners.** Thursday-Friday. Children's Orthopedic Hospital and Medical Center, Seattle. 12 hrs. $35. Contact: William O. Robertson, MD, Director of Medical Education, Children's Orthopedic Hospital, P.O. Box 5371, Seattle 98105. (206) 634-5072.

May 28-29—**Deaf-Blind Workshop.** Wednesday, Thursday. Univ. of Wash. Health Sciences Center, Seattle. Hours and fee not set. Contact: Richard L. Reimer, Asst. Dir. CME, E-305, HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

May 25-27—**Alaska State Medical Association Annual Meeting.** Sunday-Tuesday. Glacier Bay, Alaska. Contact: Mrs. Martha L. MacDermaid, Alaska State Medical Assoc., 1135 8th Ave., Anchorage, Alaska 99501.

June 6-7—**Advances in Otolaryngology and Facial Plastic Surgery.** Friday-Saturday. Virginia Mason Medical Center Auditorium, Seattle. 9 hrs. $50. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) MA 3-3700, Ext. 470.

June 12-14—**Montana Academy of Family Practice Annual Meeting.** Thursday-Saturday. Farmont Hot Springs, Gregson, Montana. Contact: Francis Bertaglio, MD, 513 Main St., Deer Lodge, Montana 59722.

June 22-25—**Pacific Northwest OB-GYN Society Annual Meeting.** Sunday-Wednesday. Sun Valley, Idaho. Contact: Ms. Sylvia Gibbons, Exec. Secretary, 1220 Boren Ave., Suite 1105, Seattle 98101. (206) 682-5119.

July 30-August 1—**Idaho Medical Association Annual Meeting.** Wednesday-Friday. The Lodge, Sun Valley, Idaho. Contact: Armand L. Bird, Exec. Director, 407 W. Bannock St., Boise, Idaho 83702.

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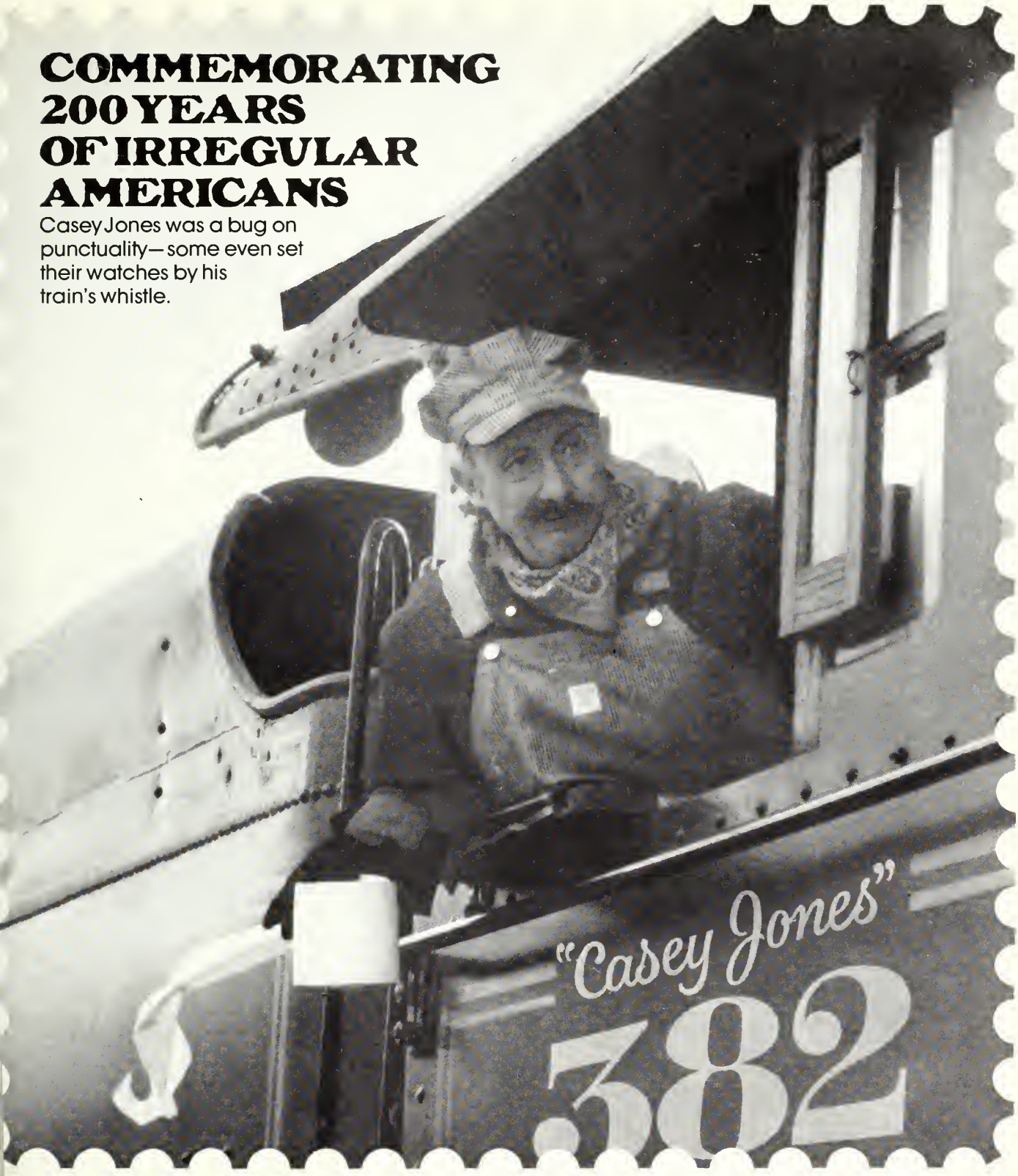
COMMEMORATING 200 YEARS OF IRREGULAR AMERICANS

Casey Jones was a bug on punctuality—some even set their watches by his train's whistle.



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Now there's Modane.® One tablet with the evening meal provides comfortable laxation in the morning...for postoperative, pregnant, or geriatric patients. Because it's **reliable.** Because it's **predictable.** Because it's **gentle.**

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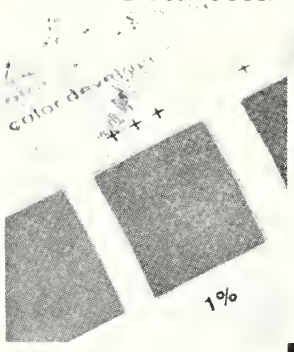

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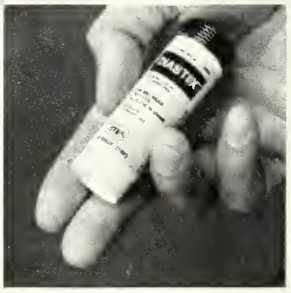

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1. Gertler, M. M., et al.: Geriatrics *25*:134-148 (May) 1970.

Indications: Based on a review of this drug by the National Academy of Sciences-National Research Council and/or other information, the FDA has classified the indications as follows:

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Adverse Reactions: On rare occasions, oral administration of the drug has been associated in time with the occurrence of severe rash. When rash appears, the drug should be discontinued. Occasional overdosage effects such as transient palpitation or dizziness are usually controlled by reducing the dose.

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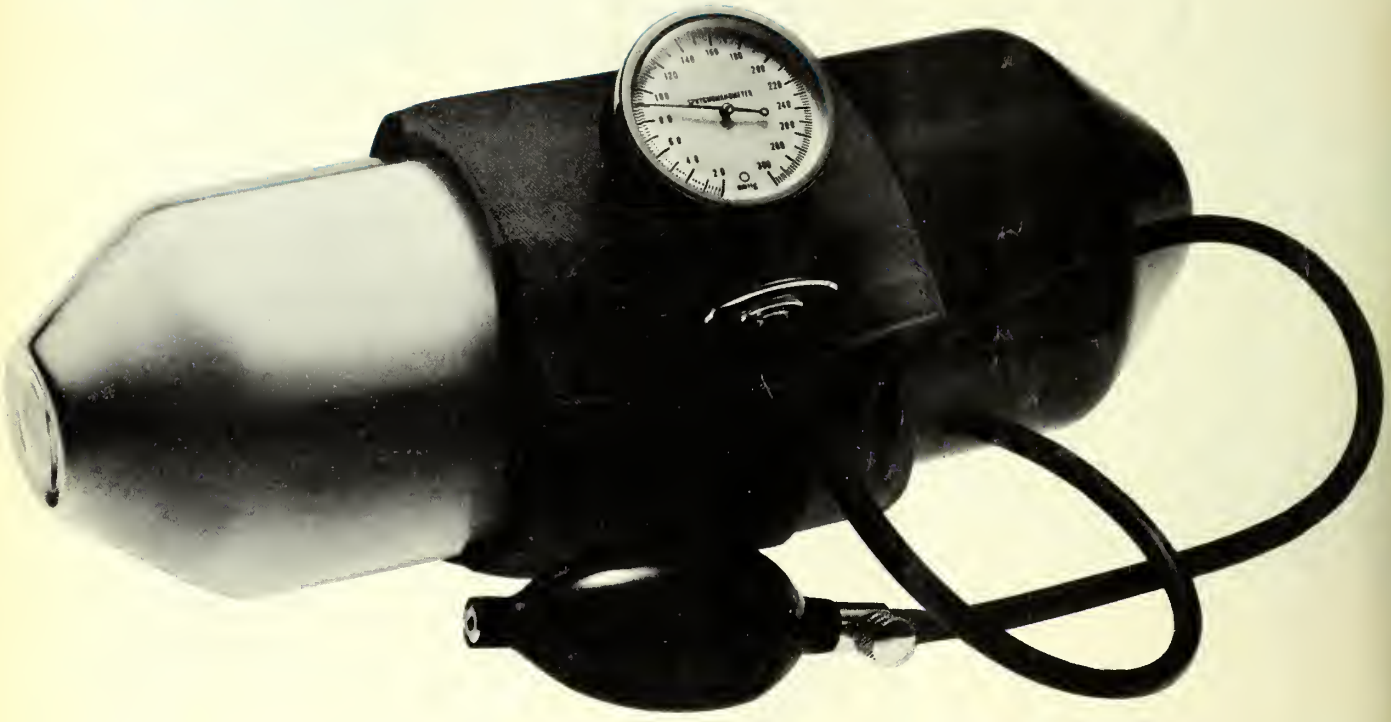

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Warnings: Do not use dietary potassium supplements or potassium salts unless hypokalemia develops or dietary potassium intake is markedly impaired. Enteric-coated potassium salts may cause small bowel stenosis with or without ulceration. Hyperkalemia (>5.4 mEq/L) has been reported in 4% of patients under 60 years, in 12% of patients over 60 years, and in less than 8% of patients overall. Rarely, cases have been associated with cardiac irregularities. Accordingly, check serum potassium during therapy, particularly in patients with suspected or confirmed renal insufficiency (e.g., elderly or diabetics). If hyperkalemia develops, substitute a thiazide alone. If spironolactone is used concomitantly with 'Dyazide', check serum potassium frequently—both can cause potassium retention and sometimes hyperkalemia. Two deaths have been reported in patients on such combined therapy (in one, recommended dosage was exceeded; in the other, serum electrolytes were not properly monitored). Observe patients on 'Dyazide' regularly for possible blood dyscrasias, liver damage or other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving Dyrenium (triamterene, SK&F). Rarely, leukopenia, thrombocytopenia, agranulocytosis, and aplastic anemia have been reported with the thiazides. Watch for signs of impending coma in acutely ill cirrhotics. Thiazides are reported to cross the placental barrier and appear in breast milk. This may result in fetal or neonatal hyperbilirubinemia, thrombocytopenia, altered carbohydrate metabolism and possibly other adverse reactions that have occurred in the adult. When used during pregnancy or in women who might bear children, weigh potential benefits against possible hazards to fetus.

Precautions: Do periodic serum electrolyte and BUN determinations. Do periodic hematologic studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in postsympathectomy patients. The following may occur: hyperuricemia and gout, reversible nitrogen retention, decreasing alkali reserve with possible metabolic acidosis, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), digitalis intoxication (in hypokalemia). Use cautiously in surgical patients. Concomitant use with antihypertensive agents may result in an additive hypotensive effect. 'Dyazide' interferes with fluorescent measurement of quinidine.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis; rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting (may indicate electrolyte imbalance), diarrhea, constipation, other gastrointestinal disturbances. Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and, rarely, allergic pneumonitis have occurred with thiazides alone.

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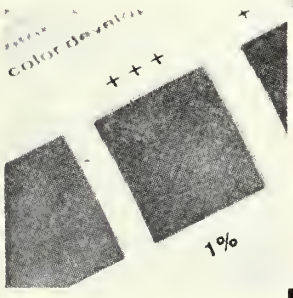

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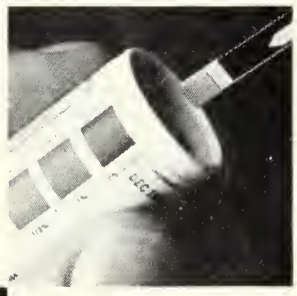

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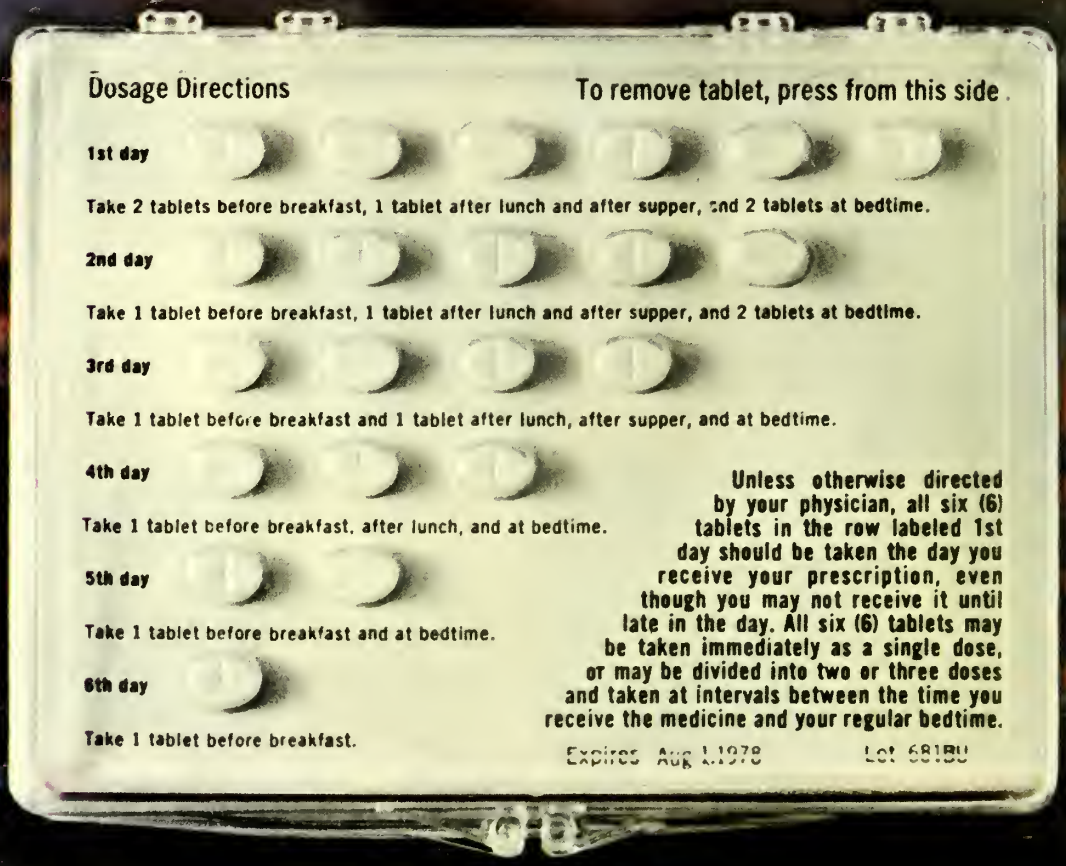

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INDICATIONS: 1. **Endocrine Disorders:** Primary or secondary adrenocortical insufficiency (hydrocortisone or cortisone is the first choice; synthetic analogs may be used in conjunction with mineralocorticoids where applicable; in infancy, mineralocorticoid supplementation is of particular importance). Congenital adrenal hyperplasia; nonsuppurative thyroiditis; hypercalcemia associated with cancer. 2. **Rheumatic Disorders:** As adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in: psoriatic arthritis; rheumatoid arthritis (selected cases may require low-dose maintenance therapy); ankylosing spondylitis; acute and subacute bursitis; acute nonspecific tenosynovitis; acute gouty arthritis. 3. **Collagen Diseases:** During an exacerbation or as maintenance therapy in selected cases of—Systemic lupus erythematosus; acute rheumatic carditis. 4. **Dermatologic Diseases:** Pemphigus; bullous dermatitis herpetiformis; severe erythema multiforme (Stevens-Johnson syndrome); exfoliative dermatitis; mycosis fungoides; severe psoriasis. 5. **Allergic States:** Control of severe or incapacitating allergic conditions intractable to adequate trials of conventional treatment: Seasonal or perennial allergic rhinitis; bronchial asthma; contact dermatitis; atopic dermatitis; serum sickness. 6. **Ophthalmic Diseases:** Severe acute and chronic allergic and inflammatory processes involving the eye and its adnexa such as—allergic corneal marginal ulcers; herpes zoster ophthalmicus; anterior segment inflammation; diffuse posterior uveitis and choroiditis; sympathetic ophthalmia; allergic conjunctivitis; keratitis; chorioretinitis; optic neuritis; iritis and iridocyclitis. 7. **Respiratory Diseases:** Symptomatic sarcoidosis; Loeffler's syndrome not manageable by other means; berylliosis; fulminating or disseminated pulmonary tuberculosis when concurrently accompanied by appropriate antituberculous chemotherapy. 8. **Hematologic Disorders:** Idiopathic and secondary thrombocytopenia in adults; acquired (autoimmune) hemolytic anemia, erythroblastopenia (RBC anemia); congenital (erythroid) hyperplastic anemia. 9. **Neoplastic Diseases:** For palliative management of: leukemias and lymphomas in adults; acute leukemia of childhood. 10. **Edematous States:** To induce a diuresis or remission of proteinuria in the nephrotic syndrome, without uremia, of the idiopathic type or that due to lupus erythematosus. 11. **Miscellaneous:** Tuberculous meningitis with subarachnoid block or impending block when concurrently accompanied by appropriate antituberculous chemotherapy. Systemic dermatomyositis (polymyositis).

CONTRAINDICATIONS: Systemic fungal infections.

WARNINGS: In patients on corticosteroid therapy subjected to unusual stress, increased dosage of rapidly acting corticosteroids before, during, and after the stressful situation is indicated.

Corticosteroids may mask some signs of infection and new infections may appear during their use. There may also be decreased resistance and inability to localize infection. Prolonged use may enhance the establishment of secondary ocular infections due to fungi or viruses.

Since adequate human reproductive studies have not been done, the use in pregnancy, nursing mothers or women of childbearing potential requires that the possible benefits be weighed against the potential hazards to the mother and the embryo or fetus. Infants should be observed for signs of hypoadrenalism.

Average and large doses of hydrocortisone or cortisone can cause elevation of blood pressure, salt and water retention, and increased excretion of potassium. These effects are less likely to occur with the synthetic derivatives except when used in large doses. Dietary salt restriction and potassium supplementation may be necessary. All corticosteroids increase calcium excretion.

While on corticosteroid therapy, patients should not be vaccinated against smallpox. Other immunization procedures should not be undertaken in patients who are on corticosteroids, especially on high dose, because of possible hazards of neurological complications and a lack of antibody response.

The use of corticosteroids in active tuberculosis should be restricted to those cases of fulminating or disseminated tuberculosis in which the corticosteroid is used for the management of the disease in conjunction with an appropriate antituberculous regimen.

If corticosteroids are indicated in patients with latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation of the disease may occur. During prolonged corticosteroid therapy, these patients should receive chemoprophylaxis.

PRECAUTIONS: Hormone therapy is an adjunct to, and not a replacement for, conventional therapy.

Dosage should be individualized according to the severity of the disease and the response of the patient. As soon as a satisfactory clinical response is obtained, the daily dose should be reduced, either to termination of treatment or to the minimal effective maintenance dose level. The lowest possible dose should be used and when reduction in dosage is possible, the reduction should be gradual if the drug has been administered for more than a few days. If a period of spontaneous remission occurs in a chronic condition, treatment should be discontinued.

Drug-induced secondary adrenocortical insufficiency may be minimized by gradual reduction of dosage. This type of relative insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress occurring during that period, hormone therapy should be reinstituted. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently.

There is an enhanced effect of corticosteroids on patients with hypothyroidism and in those with cirrhosis.

Corticosteroids should be used cautiously in patients with ocular herpes simplex because of possible corneal perforation.

Psychic derangements may appear or existing emotional instability or psychotic tendencies may be aggravated by corticosteroids.

Aspirin should be used cautiously in conjunction with corticosteroids in hypoprothrombinemia.

Steroids should be used with caution in nonspecific ulcerative colitis, if there is a probability of impending perforation, abscess or other pyogenic infection; diverticulitis; fresh intestinal anastomoses; active or latent peptic ulcer; renal insufficiency; hypertension; osteoporosis; and myasthenia gravis.

Growth and development of infants and children on prolonged corticosteroid therapy should be carefully observed.

Blood pressure, body weight, routine laboratory studies, including 2-hour postprandial blood glucose and serum potassium, and a chest X-ray should be obtained at regular intervals during prolonged therapy. Upper GI X-rays are desirable in patients with known or suspected peptic ulcer disease.

ADVERSE REACTIONS: Fluid and Electrolyte Disturbances. Sodium retention; fluid retention; congestive heart failure in susceptible patients; potassium loss; hypokalemic alkalosis; hypertension. **Musculoskeletal.** Muscle weakness; steroid myopathy; loss of muscle mass; osteoporosis; vertebral compression fractures; aseptic necrosis of femoral and humeral heads; pathologic fracture of long bones. **Gastrointestinal.** Peptic ulcer with possible perforation and hemorrhage; pancreatitis; abdominal distention; ulcerative esophagitis. **Dermatologic.** Impaired wound healing; thin fragile skin; petechiae and ecchymoses; facial erythema; increased sweating. May suppress reactions to skin tests. **Neurological.** Increased intracranial pressure with papilledema (pseudotumor cerebri) usually after treatment. Convulsions; vertigo; headache. **Endocrine.** Development of Cushingoid state; suppression of growth in children; secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress, as in trauma, surgery or illness; menstrual irregularities; decreased carbohydrate tolerance; manifestations of latent diabetes mellitus; increased requirements for insulin or oral hypoglycemic agents in diabetics. **Ophthalmic.** Posterior subcapsular cataracts; increased intraocular pressure; glaucoma; exophthalmos. **Metabolic.** Negative nitrogen balance due to protein catabolism.

DOSAGE AND ADMINISTRATION: The initial dosage may vary from 4 to 48 mg per day. **Requirements are variable and must be individualized on the basis of the disease under treatment and the response of the patient.** The proper maintenance dosage should be determined by decreasing the initial dosage in small decrements at appropriate time intervals until the lowest dosage which will maintain an adequate clinical response is reached. If after long-term therapy the drug is to be stopped, it is recommended that it be withdrawn gradually rather than abruptly.

ALTERNATE-DAY THERAPY (ADT): ADT is a corticosteroid dosing regimen in which twice the usual daily dose of corticoid is administered every other morning. The purpose of this mode of therapy is to provide the patient requiring long-term pharmacologic dose treatment with the beneficial effects of corticoids while minimizing certain undesirable effects including pituitary-adrenal suppression, the Cushingoid state, corticoid withdrawal symptoms, and growth suppression in children.

Medrol (methylprednisolone) or other short-acting (producing adrenocortical suppression for 1¼ to 1½ days following a single dose) corticoids are recommended for ADT. Complete control of symptoms will not be possible in all patients. When considering this mode of therapy, keep in mind the basic principles and indications for corticosteroid therapy. The benefits of ADT should not encourage the indiscriminate use of steroids.

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MED B-8-S (MAG)

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Short-term, adjunctive, corticosteroid therapy

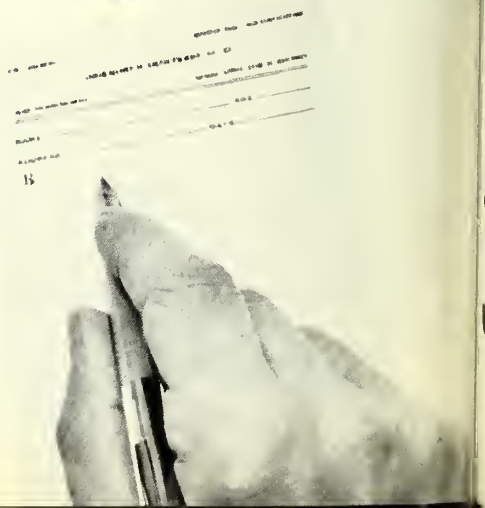
Medrol® 4 mg Dosepak™

(methylprednisolone)

©1974 The Upjohn Company

Upjohn The Upjohn Company, Kalamazoo, Michigan 49001

Bioequivalence



the weight of scientific opinion:

If the pharmacist substituted a chemically equivalent drug for the one you have specified for your patient—could you be certain of that product's safety and effectiveness simply because the chemical content was the same?

Definitely not, unless bioequivalence tests and other quality assurance checks had been conducted. The pharmaceutical industry and many scientists have maintained this position for years, but others have questioned it. Now the Office of Technology Assessment of the Congress of the United States has reported on the issue in its Drug Bioequivalence Study.*

Here are a few definitive statements in the O.T.A. report:

"...the problem of bioinequivalency in chemically equivalent products is a real one. Since the studies in which lack of bioequivalence was demonstrated involved marketed products that met current compendial standards, these documented instances constitute unequivocal evidence that neither the present standards for testing the finished product nor the specifications for materials, manufacturing process, and controls are adequate to ensure that ostensibly equivalent drug products are, in fact, equivalent in bioavailability.

"While these therapeutic failures resulting from problems of bioavailability were recognized and well documented, it is entirely possible that other therapeutic failures and/or instances of toxicity that had a similar basis have escaped attention."

The Pharmaceutical Manufacturers Association supports federal legislative amendments that would require manufacturers of duplicate prescription pharmaceutical products, subject to new drug procedures, to document:

(a) chemical equivalence; and (b) biological equivalence, where bioavailability test methods have been validated as a reliable means of assuring clinical equivalence; or (c) where such validation is not possible, therapeutic equivalence.

In addition, the PMA supports federal legislation that would require certification of all manufacturers of prescription products before they could start in business, annual inspections and certification thereafter, and strict adherence to FDA regulations on good manufacturing practices.

The overall quality of the United States drug supply is excellent. But only a total quality assurance program, envisaged in these and other policy positions adopted by the PMA Board of Directors in 1974, can bring about acceptable levels of performance by all prescription drug manufacturers and thereby assure the integrity of your prescription...

P·M·A

Pharmaceutical Manufacturers Association
1155 Fifteenth Street, N.W.
Washington, D.C. 20005

*Copies of the complete report on Drug Bioequivalence may be obtained from the Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402.

protecting the integrity of your prescription

"Antiacid" action for ulcer patients...

one of the many things you need in an anticholinergic.

Pro-Banthīne is considered adjunctive in total peptic ulcer therapy that may include diet, conventional antacids, bed rest, and other supportive measu

Pro-Banthīne is provided in several different dosage forms which will me virtually any clinical need. It is just as versatile in filling patient needs, amor which are:

"Antiacid" action—Pro-Banthīne® (propantheline bromide) reduces gas secretory volume and resting total an free acid.

"Analgesic" action—Pro-Banthīne he to control the acid-spasm-pain comple

Vigorous anticholinergic action—Pro-Banthīne® Vials, 30 mg., are for intramuscular or intravenous use whe prompt and vigorous anticholinergic action is required.

Mild anticholinergic action—Pro-Banthīne® Half Strength, 7.5 mg. tablets, for more exact adjustment of maintenance dosage in mild to moderate gastrointestinal disorders.

Pro-Banthīn
(propantheline bromide)

a good option in peptic ulcer

Pro-Banthīne®
brand of
propantheline bromide

ons: Pro-Banthīne is effective as
ive therapy in the treatment of peptic
osage must be adjusted to the
ial.

ndications: Glaucoma, obstructive
of the gastrointestinal tract,
tive uropathy, intestinal atony, toxic
olon, hiatal hernia associated with
sophagitis, or unstable cardiovascular
nent in acute hemorrhage.

gs: Patients with severe cardiac
should be given this medication
ution. Fever and possibly heat stroke
cur due to anhidrosis.

sage may cause a curare-like action,
s of voluntary muscle control.
h patients prompt and continuing
l respiration should be applied until
g effect has been exhausted.
a in an ileostomy patient may indicate
tion, and this possibility should be con-
l before administering Pro-Banthīne.

tions: Since varying degrees of urinary
cy may be evidenced by elderly males
ostatic hypertrophy, such patients
be advised to micturate at the time
g the medication.

sage should be avoided in patients
y ill with ulcerative colitis.

e *Reactions:* Varying degrees of
of salivary secretions may occur as
mydriasis and blurred vision. In
n the following adverse reactions have
eported: nervousness, drowsiness,
ss, insomnia, headache, loss of the
of taste, nausea, vomiting, constipation,
nce and allergic dermatitis.

e and Administration: The
mended daily dosage for adult oral
y is one 15-mg. tablet with meals and
bedtime. Subsequent adjustment to
ient's requirements and tolerance
e made.

upplied: Pro-Banthīne is supplied as
of 15 and 7.5 mg., as prolonged-
tablets of 30 mg. and, for parenteral
serum-type vials of 30 mg.

LE **Searle & Co.**
San Juan, Puerto Rico 00936

medical inquiries to: G. D. Searle & Co.
Department, Box 5110, Chicago, Ill. 60680 481

The Pain Phone

When a telephone prescription for pain relief is necessary or convenient, you can call in your order for Empirin Compound with Codeine in 45 of the 50 states† That includes No. 4, which provides a full grain of codeine for more intense, acute pain.

† The exceptions: Alaska, Arizona, Maine, Oregon, Rhode Island, and the District of Columbia.

EMPIRIN® COMPOUND c̄ CODEINE

No. 4 codeine phosphate* (64.8 mg) gr 1

No. 3 codeine phosphate* (32.4 mg) gr ½

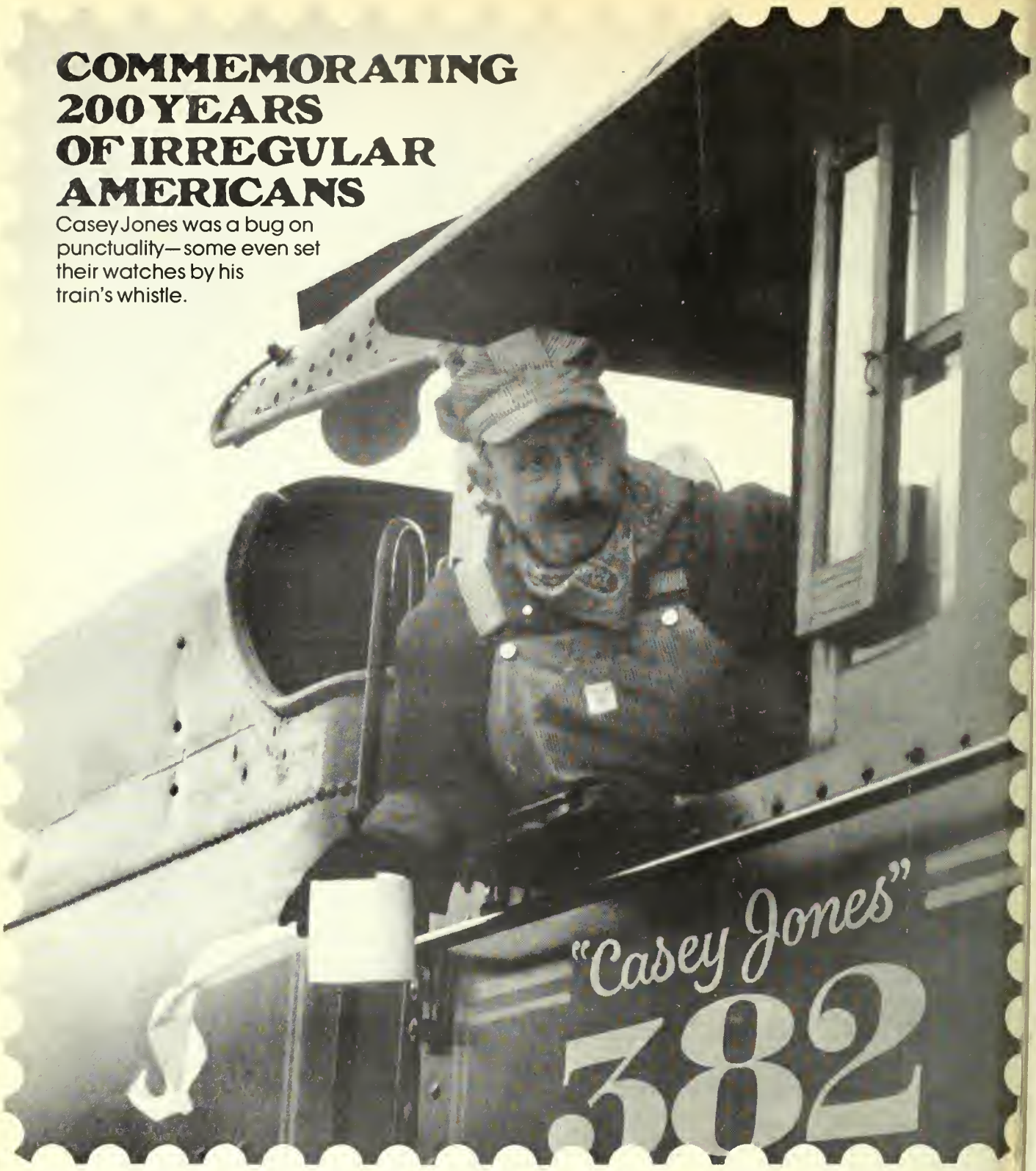
Each tablet also contains aspirin gr 3½, phenacetin gr 2½, caffeine gr ½.
*Warning—may be habit-forming.

CIII

Wellcome **Burroughs Wellcome Co.**
Research Triangle Park
North Carolina 27709

COMMEMORATING 200 YEARS OF IRREGULAR AMERICANS

Casey Jones was a bug on punctuality—some even set their watches by his train's whistle.



Just get me to the station on time. For 200 years, Americans have been in a hurry. But some things just don't happen on schedule—like bowel movements in a constipated patient. And for 200 years, Americans have dealt with this problem in a variety of ways—and with varying degrees of success.

Now there's Modane.® One tablet with the evening meal provides comfortable laxation in the morning...for postoperative, pregnant, or geriatric patients. Because it's **reliable.** Because it's **predictable.** Because it's **gentle.**

MODANE®

LAXATIVE TABLETS

WARREN-TEED
PHARMACEUTICALS INCORPORATED
SUBSIDIARY OF ROHM AND HAAS COMPANY
COLUMBUS, OHIO 43215

Something new in investing and saving.

The Union Bank Money Market Savings Account.

Tailored to the fast-changing times, this Union Bank account combines the savings and investment functions for the first time. Helps you earn the maximum yield with security, liquidity and flexibility. Makes it simple for the substantial saver to invest in the money market. Gives the short-term investor professional assistance with speed, convenience and free services.

1. HIGHER YIELD ON SAVINGS. Union Bank pays a higher return on regular savings than any of the other five major California banks.

2. NO-FEE MARKET TRANSACTIONS. Buy or sell Treasury bills or other money market investments simply by calling Union Bank. Eight free transactions per year per account.

3. FACTS BY PHONE. Up-to-the-minute quotations and information on the money market by calling a special number.

4. BACKGROUND INFORMATION. Bi-weekly Money Market Newsletter prepared by the Bank's investment specialists.

5. FREE SAFEKEEPING. Securities may be kept in Union Bank's vaults without charge.

6. MONTHLY STATEMENT. You receive a detailed monthly statement of securities in your portfolio—in addition to a regular quarterly savings statement.

SAVINGS BALANCE REQUIREMENT: $10,000 *(quarterly average).*

THE BUSINESS BANK
(with special advantages for investor/savers)

John Dorman W-1
Money Market Savings Department
Union Bank
P.O. Box 3100, Terminal Annex
Los Angeles, California 90051

Please send me the facts on the new Union Bank Money Market Savings Account.

Name_____

Address_____

City_____ Zip_____

☐ Please contact me.

Home phone_____ Bus. phone_____

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The 2 most widely prescribed sodium levothyroxine (T_4) products are:

LETTER®
(Sodium levothyroxine, Armour) Tablets

SYNTHROID®
(Sodium levothyroxine) Flint Tablets

LETTER® IS 10% LOWER IN PRICE THAN SYNTHROID®*

Armour Pharmaceutical Company
Phoenix, Arizona 85077

*Armour's published list price to pharmacies for LETTER is 10% less than the Flint published price for Synthroid in bottles of 100 of the same strength. Pharmacy charges to the patient will vary from pharmacy to pharmacy, depending on individual locations, policies and services offered.

PROLOID® (thyroglobulin)

Caution: Federal law prohibits dispensing without prescription.

Description. Proloid (thyroglobulin) is obtained from a purified extract of frozen hog thyroid. It contains the known calorigenically active components, Sodium Levothyroxine (T_4) and Sodium Liothyronine (T_3). Proloid (thyroglobulin) conforms to the primary USP specifications for desiccated thyroid—for iodine based on chemical assay—and is also biologically assayed and standardized in animals.

Chromatographic analysis to standardize the Sodium Levothyroxine and Sodium Liothyronine content of Proloid (thyroglobulin) is routinely employed.

The ratio of T_4 and T_3 in Proloid (thyroglobulin) is approximately 2.5 to 1.

Proloid (thyroglobulin) is stable when stored at usual room temperature.

Indications. Proloid (thyroglobulin) is thyroid replacement therapy for conditions of inadequate endogenous thyroid production: e.g., cretinism and myxedema. Replacement therapy will be effective only in manifestations of hypothyroidism.

In simple (nontoxic) goiter, Proloid (thyroglobulin) may be tried therapeutically, in nonemergency situations, in an attempt to reduce the size of such goiters.

Contraindication. Thyroid preparations are contraindicated in the presence of uncorrected adrenal insufficiency.

Warnings. Thyroglobulin should not be used in the presence of cardiovascular disease unless thyroid-replacement therapy is clearly indicated. If the latter exists, low doses should be instituted beginning at 0.5 to 1.0 grain (32 to 64 mg) and increased by the same amount in increments at two-week intervals. This demands careful clinical judgment.

Morphologic hypogonadism and nephroses should be ruled out before the drug is administered. If hypopituitarism is present, the adrenal deficiency must be corrected prior to starting the drug.

Myxedematous patients are very sensitive to thyroid and dosage should be started at a very low level and increased gradually.

Precaution. As with all thyroid preparations this drug will alter results of thyroid function tests.

Adverse Reactions. Overdosage or too rapid increase in dosage may result in signs and symptoms of hyperthyroidism, such as menstrual irregularities, nervousness, cardiac arrhythmias, and angina pectoris.

Dosage and Administration. Optimal dosage is usually determined by the patient's clinical response. Confirmatory tests include BMR, $T_3{}^{131}I$ resin sponge uptake, $T_3{}^{131}I$ red cell uptake, Thyro Binding Index (TBI), and Achilles Tendon Reflex Test. Clinical experience has shown that a normal PBI (3.5-8 mcg/100 ml) will be obtained in patients made clinically euthyroid when the content of T_4 and T_3 is adequate. Dosage should be started in small amounts and increased gradually with increments at intervals of one to two weeks. Usual maintenance dose is 0.5 to 3.0 grains (32 to 190 mg) daily.

Instructions for Use. The following conversion table lists the approximate equivalents of other thyroid preparations to Proloid (thyroglobulin) when changing medication from desiccated thyroid, T_4 (sodium levothyroxine), T_3 (sodium liothyronine), or T_4/T_3 (liotrix).

CONVERSION TABLE

Dose of Proloid (thyroglobulin)	Dose of Desiccated Thyroid	Dose of T_4 (sodium levothyroxine)	Dose of T_3 (sodium liothyronine)	Dose of liotrix (T_4/T_3)
1 grain	1 grain	0.1 mg	25 mcg	#1 (60 mcg/15 mcg)
2 grains	2 grains	0.2 mg	50 mcg	#2 (120 mcg/30 mcg)
3 grains	3 grains	0.3 mg	75 mcg	#3 (180 mcg/45 mcg)
4 grains	4 grains	0.4 mg	100 mcg	
5 grains	5 grains	0.5 mg	125 mcg	

In changing from Thyroid USP to Proloid (thyroglobulin), substitute the equivalent dose of Proloid (thyroglobulin). Each patient may still require fine adjustment of dosage because the equivalents are only estimates.

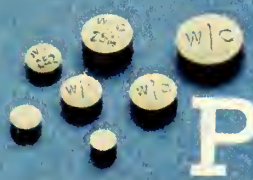
Overdosage Symptoms. Headache, instability, nervousness, sweating, tachycardia, with unusual bowel motility. Angina pectoris or congestive heart failure may be induced or aggravated. Shock may develop. Massive overdosage may result in symptoms resembling thyroid storm. Chronic excessive dosage will produce the signs and symptoms of hyperthyroidism.

(Treatment: In shock, supportive measures should be utilized. Treatment of unrecognized adrenal insufficiency should be considered.)

Supplied. ¼ grain tablets in bottles of 100 (N0047-0250-51) and 1000 (N0047-0250-60); ½ grain tablets in bottles of 100 (N0047-0251-51) and 1000 (N0047-0251-60); scored 1 grain tablets in bottles of 100 (N0047-0252-51) and 1000 (N0047-0252-60); 1½ grain tablets in bottles of 100 (N0047-0253-51) and 1000 (N0047-0253-60); scored 2 grains tablets in bottles of 100 (N0047-0257-51); 3 grain tablets in bottles of 100 (N0047-0254-51) and 1000 (N0047-0254-60); scored 5 grain tablets in bottles of 100 (N0047-0255-51) and 1000 (N0047-0255-60). Full information is available on request. P-GP-51 4/c

WARNER/CHILCOTT
Division, Warner-Lambert Company
Morris Plains, N.J. 07950

Improving on nature...
from the rough, uncut stone
to the finished gem



In thyroid therapy, too...
all the qualities of the "natural" with the added improvements of man...

Proloid®
(thyroglobulin)

natural thyroid...but uniquely purified
Devoid of any glandular debris.

natural thyroid...but triply standardized
Standardized chemically, biologically, and (at intervals) clinically, for consistent metabolic activity from batch to batch.

natural thyroid...but consistently fresh
Potency undiminished for up to 4 years under proper storage conditions.

It all adds up to natural thyroid with the added improvements of man.

Please see adjoining column for brief summary of prescribing information.

PreSun®

(5% PABA LOTION)

may help prevent harmful effects of the sun such as premature aging of skin and skin cancer.*

*Information on file at Westwood Pharmaceuticals Inc.

WESTWOOD
PHARMACEUTICALS INC.
Buffalo, New York 14213

©1974, W. P. Inc.

Maybe the patient's self-diagnosis is right. He could have hay fever. But that bright red nasal mucosa, along with the thick discharge and excoriation around the nares, strongly suggests that the main problem is a cold. Hay fever or another form of allergic rhinitis may or may not be an underlying factor.

If a complete history and examination rule out allergic rhinitis, the long-term outlook will be a lot more favorable than his own "diagnosis" would have indicated.

But right now, whether he's got allergic rhinitis or a cold, he's suffering from the same irritating symptoms of drip, congestion and stuffiness. Try DIMETAPP EXTENTABS®. They're formulated to relieve these symptoms without much chance of causing drowsiness or overstimulation. Your patients will appreciate the 24-hour relief they can get from just one tablet every 12 hours.

Cold or

Allergy?

Whether it's a cold or an allergy, Dimetapp Extentabs® effectively relieve stuffiness, drip and congestion.

INDICATIONS: Dimetapp Extentabs are indicated for symptomatic relief of allergic manifestations of upper respiratory illnesses, such as the common cold, seasonal allergies, sinusitis, rhinitis, conjunctivitis and otitis. In these cases it quickly reduces inflammatory edema, nasal congestion and excessive upper respiratory secretions, thereby affording relief from nasal stuffiness and postnasal drip.

CONTRAINDICATIONS: Hypersensitivity to antihistamines of the same chemical class. Dimetapp Extentabs are contraindicated during pregnancy and in children under 12 years of age. Because of its drying and thickening effect on the lower respiratory secretions, Dimetapp is not recommended in the treatment of bronchial asthma. Also, Dimetapp Extentabs are contraindicated in concurrent MAO inhibitor therapy.

WARNINGS: *Use in children:* In infants and children [illegible] in overdosage may pr[illegible] and death

PRECAUTIONS: Ad[illegible] patients with cardiac [illegible] lar diseases or hyper[illegible] patient's response [illegible] he should be cautioned [illegible] in operation [illegible] driving an automobile [illegible] chinery, etc. Patients re[illegible] mines should be warned [illegible] additive effects with CNS depressants.

[illegible]

Dimetapp Extentabs®

Dimetane® (brompheniramine maleate), 12 mg.; phenylephrine HCl, 15 mg.; phenylpropanolamine HCl, 15 mg.

A·H·ROBINS

A. H. Robins Company, Richmond, Va. 23220

when pain goes on... and on... and on–

For the patient with a terminal illness, PAIN past, present, and future can dominate his thoughts until it becomes almost an obsession. The more he is aware of the pain he is now experiencing, the more difficult it is to erase his memory of yesterday's pain, and to allay his fearful anticipation of tomorrow's pain.

Surely the last thing this patient needs is an analgesic containing caffeine to stimulate the senses and heighten pain awareness. A far more logical choice is Phenaphen with Codeine. The sensible formula provides ¼ grain of phenobarbital to take the nervous "edge" off, so the rest of the formula can help control the pain more effectively. Don't you agree, Doctor, that psychic distress is an important factor in most of your terminal and long-term convalescent patients?

the analgesic formula that calms instead of caffeinates

Phenaphen® with Codeine

Phenaphen with Codeine No. 2, 3, or 4 contains: Phenobarbital (¼ gr.), 16.2 mg. (warning: may be habit forming); Aspirin (2½ gr.), 162.0 mg.; Phenacetin (3 gr.), 194.0 mg.; Codeine phosphate, ¼ gr. (No. 2), ½ gr. (No. 3) or 1 gr. (No. 4) (warning: may be habit forming).

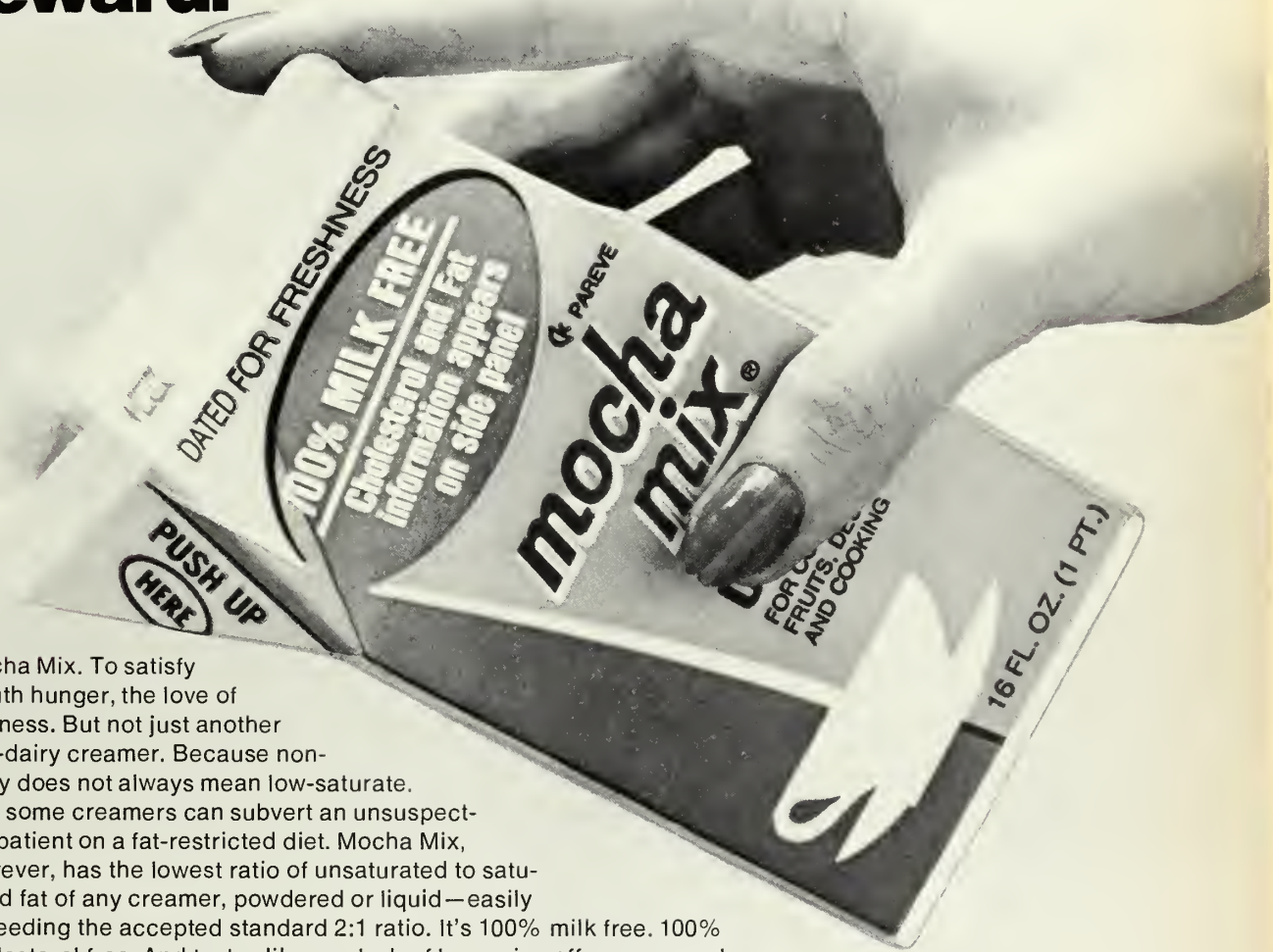
Indications: Provides relief in severer grades of pain, on low codeine dosage, with minimal possibility of side effects. Its use frequently makes unnecessary the use of addicting narcotics. **Contraindications:** Hypersensitivity to any of the components. **Precautions:** As with all phenacetin-containing products, excessive or prolonged use should be avoided. **Side effects:** Side effects are uncommon, although nausea, constipation and drowsiness may occur. **Dosage:** Phenaphen No. 2 and No. 3—1 or 2 capsules every 3 to 4 hours as needed; Phenaphen No. 4—1 capsule every 3 to 4 hours as needed. For further details see product literature.

(III) Phenaphen with Codeine is now classified in Schedule III, Controlled Substances Act of 1970. Available on written or oral prescription and may be refilled 5 times within 6 months, unless restricted by state law.

A. H. Robins Company, Richmond, Va. A·H·ROBINS

What to do when your patient feels robbed of milk, cream and saturated fat.

Offer a reward.



Mocha Mix. To satisfy mouth hunger, the love of richness. But not just another non-dairy creamer. Because non-dairy does not always mean low-saturate. And some creamers can subvert an unsuspecting patient on a fat-restricted diet. Mocha Mix, however, has the lowest ratio of unsaturated to saturated fat of any creamer, powdered or liquid—easily exceeding the accepted standard 2:1 ratio. It's 100% milk free. 100% cholesterol free. And tastes like a splash of luxury in coffee, on cereal, fruit, dessert, even in cooking. If you must deprive your patient, add a reward for good behavior. Mocha Mix.

MOCHA MIX DATA SHEET

Portion Size 1 Fluid Ounce (2 Tbs.)

Servings per container	16
Calories	40
Protein	0 grams
Carbohydrate	3 grams
Fat	3 grams
Percent of Calories from Fat	73%
Polyunsaturated Fat	1 gram
Saturated Fat	0 grams
Cholesterol	0

(Percentage of U.S. Recommended Daily Allowances (U.S., RDA)*

*Contains less than 2% of the U.S. RDA of Protein, Vitamin A, Vitamin C, Thiamine, Riboflavin, Niacin, Calcium, Iron.

In addition to the pint and quart size found in the dairy case of most grocery stores, Mocha Mix is available in 4 ounce and ½ oz. portion packs for hospitals and institutions.

Interested? Send us a note and we will send you a supply of coupons your patients can redeem at their grocers. Hospital service may also be supplied upon request. Mail to:

Mocha Mix Dept. Presto Food Products, Inc.
P.O. Box No. 21908, Los Angeles, Calif. 90021

mocha mix® ...the non-dairy creamer that's lowest in saturated fat.

IN GONORRHEA

INJECTION

Wycillin®

(STERILE PROCAINE PENICILLIN G SUSPENSION) WYETH

In **Gonorrhea,** the drug regimen of choice is aqueous procaine penicillin G. In uncomplicated cases, administration of 4.8 million units together with 1 gram oral probenecid, given at least 30 minutes prior to injection, is recommended.

Indications: In treatment of moderately severe infections due to penicillin G-sensitive microorganisms sensitive to the low and persistent serum levels common to this particular dosage form. Therapy should be guided by bacteriological studies (including sensitivity tests) and by clinical response.

NOTE: When high sustained serum levels are required use aqueous penicillin G, IM or IV.

The following infection will usually respond to adequate dosages of intramuscular procaine penicillin G.—*N. gonorrhoeae:* acute and chronic (without bacteremia).

For deep intramuscular injection only.

Contraindication: Previous hypersensitivity reaction to any penicillin.

Warnings: Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy.

Serious anaphylactoid reactions require immediate emergency treatment with epinephrine. Oxygen and intravenous corticosteroids should also be administered as indicated.

Although anaphylaxis is more frequent following parenteral therapy it has occurred in patients on oral penicillins. These reactions are more apt to occur in individuals with a history of sensitivity to multiple allergens.

There have been well documented reports of individuals with a history of penicillin hypersensitivity reactions who have experienced severe hypersensitivity reactions when treated with a cephalosporin. Before therapy with a penicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, and other allergens. If an allergic reaction occurs, the drug should be discontinued and the patient treated with the usual agents e.g., pressor amines, antihistamines and corticosteroids.

Mental disturbances, including anxiety, confusion, agitation, depression, and hallucinations, have been reported in individuals following single-dose schedules for gonorrhea. Reactions have been transient, lasting from 15-30 minutes.

Precautions: Use cautiously in individuals with histories of significant allergies and/or asthma.

Carefully avoid intravenous or intraarterial use, or injection into or near major peripheral nerves or blood vessels, since such injections may produce neurovascular damage.

A small percentage of patients are sensitive to procaine. If there is a history of sensitivity, make the usual test: Inject intradermally 0.1 cc. of a 1 to 2 percent procaine solution. Development of an erythema, wheal, flare or eruption indicates procaine sensitivity. Sensitivity should be treated by the usual methods, including barbiturates, and procaine penicillin preparations should not be used. Antihistaminics appear beneficial in treatment of procaine reaction.

The use of antibiotics may result in overgrowth of nonsusceptible organisms. Constant observation of the patient is essential. If new infections due to bacteria or fungi appear during therapy, discontinue penicillin and take appropriate measures.

If allergic reaction occurs, withdraw penicillin unless, in the opinion of the physician, the condition being treated is life threatening and amenable only to penicillin therapy.

When treating gonococcal infections with suspected primary or secondary syphilis, perform proper diagnostic procedures, including darkfield examinations. In all cases in which concomitant syphilis is suspected, perform monthly serological tests for at least four months.

Adverse Reactions: (Penicillin has significant index of sensitization) skin rashes, ranging from maculopapular eruptions to exfoliative dermatitis; urticaria; serum sickness-like reactions, including chills, fever, edema, arthralgia and prostration. Severe and often fatal anaphylaxis has been reported. (See "Warnings.")

As with other antisyphilitics, Jarisch-Herxheimer reaction has been reported.

Dosage and Administration: Administer only by *deep intramuscular injection,* in upper outer quadrant of buttock. In infants and small children, midlateral aspect of thigh may be preferable. When doses are repeated, vary injection site. Before injection, aspirate to be sure needle bevel is not in blood vessel. If blood appears, remove needle and inject in another site.

Although some isolates of *Neisseria gonorrhoeae* have decreased susceptibility to penicillin, this resistance is relative, not absolute, and penicillin in large doses remains the drug of choice. Physicians are cautioned not to use less than recommended doses.

Gonorrheal infections (uncomplicated)—Men or Women: 4.8 million units intramuscularly divided into at least two doses and injected at different sites at one visit, together with 1 gram of oral probenecid, preferably given at least 30 minutes prior to injection.

NOTE: Treatment of severe complications of gonorrhea should be individualized using large amounts of short-acting penicillin. Gonorrheal endocarditis should be treated intensively with aqueous penicillin G. Prophylactic or epidemiologic treatment for gonorrhea (male and female) is accomplished with same treatment schedules as for uncomplicated gonorrhea.

Retreatment: The National Center for Disease Control, Venereal Disease Branch, U.S. Dept. H.E.W. recommends:

Test cure procedures at approximately 7-14 days after therapy. In the male, a gram-stained smear is adequate if positive; otherwise, a culture specimen should be obtained from the anterior urethra. In the female, culture specimens should be obtained from both the endocervical and anal canal sites.

Retreatment in males is indicated if urethral discharge persists 3 or more days following initial therapy and smear or culture remains positive. Follow-up treatment consists of 4.8 million units aqueous procaine penicillin G, I.M. divided in 2 injection sites at single visit.

In uncomplicated gonorrhea in the female, retreatment is indicated if follow-up cervical or rectal cultures remain positive for *N. gonorrhoeae.* Follow-up treatment consists of 4.8 million units aqueous procaine penicillin G daily on 2 successive days.

Syphilis: all gonorrhea patients should have a serologic test for syphilis at the time of diagnosis. Patients with gonorrhea who also have syphilis should be given additional treatment appropriate to the stage of syphilis.

Composition: Each disposable syringe 2,400,000 units (4-cc. size) contains procaine penicillin G in a stabilized aqueous suspension with sodium citrate buffer, and as w/v approximately 0.5% lecithin, 0.5% carboxymethylcellulose, 0.5% povidone, 0.1% methylparaben, and 0.01% propylparaben. The multiple-dose 10-cc. vial contains per cc. 300,000 units procaine penicillin G in a stabilized aqueous suspension with sodium citrate buffer and approximately 7 mg. lecithin, 2 mg. carboxymethylcellulose, 3 mg. povidone, 0.5 mg. sorbitan monopalmitate, 0.5 mg. polyoxyethylene sorbitan monopalmitate, 1.2 mg. methylparaben, and 0.14 mg. propylparaben.

Five are graduating with honors. How many with VD?

On the average, you can figure the incidence of VD among teenagers at about 900 per 100,000 population.* And growing.

Among those in the 20-24 age-group, the incidence is even higher. And it, too, is growing.

In the long run, a populace educated to the risks and prevention of VD is probably the best answer to the problem. Meanwhile, though, adequate doses of the recommended types of penicillin remain a formidable weapon.

IN SYPHILIS
INJECTION
Bicillin® L-A
(STERILE BENZATHINE PENICILLIN G SUSPENSION) WYETH

Syphilis is preferably treated with benzathine penicillin G, which is also the drug of choice for prophylaxis after exposure. Administration of 2.4 million units (1.2 million in each buttock) usually cures most cases of primary, secondary and latent syphilis with negative spinal fluid.

Indications: In treatment of infections due to penicillin G-sensitive microorganisms that are susceptible to the low and very prolonged serum levels common to this particular dosage form. Therapy should be guided by bacteriological studies (including sensitivity tests) and by clinical response.

The following infections will usually respond to adequate dosage of intramuscular benzathine penicillin G.—Venereal infections: Syphilis, yaws, bejel and pinta.

For deep intramuscular injection only.

Contraindication: Previous hypersensitivity reaction to any penicillin.

Warnings: Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported. Anaphylaxis is more frequent following parenteral therapy but has occurred with oral penicillins. These reactions are more apt to occur in individuals with history of sensitivity to multiple allergens.

Severe hypersensitivity reactions with cephalosporins have been well documented in patients with history of penicillin hypersensitivity. Before penicillin therapy, carefully inquire into previous hypersensitivity to penicillins, cephalosporins and other allergens. If allergic reaction occurs, discontinue drug and treat with usual agents, e.g., pressor amines, antihistamines and corticosteroids.

Precautions: Use cautiously in individuals with histories of significant allergies and/or asthma.

Carefully avoid intravenous or intraarterial use, or injection into or near major peripheral nerves or blood vessels, since such injection may produce neurovascular damage.

In streptococcal infections, therapy must be sufficient to eliminate the organism; otherwise the sequelae of streptococcal disease may occur. Take cultures following completion of treatment to determine whether streptococci have been eradicated.

Prolonged use of antibiotics may promote overgrowth of nonsusceptible organisms including fungi. Take appropriate measures should superinfection occur.

Adverse Reactions: Hypersensitivity reactions reported are skin eruptions (maculopapular to exfoliative dermatitis), urticaria and other serum sickness-like reactions, laryngeal edema and anaphylaxis. Fever and eosinophilia may frequently be only reaction observed. Hemolytic anemia, leucopenia, thrombocytopenia, neuropathy and nephropathy are infrequent and usually associated with high doses of parenteral penicillin.

As with other antisyphilitics, Jarisch-Herxheimer reaction has been reported.

Dosage and Administration: Venereal infections—

Syphilis—Primary, secondary and latent—2.4 million units (1 dose).

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Congenital—under 2 years of age, 50,000 units/Kg. body weight; ages 2-12 years, adjust dosage based on adult dosage schedule.

(Shake multiple-dose vial vigorously before withdrawing the desired dose.) Administer by **deep intramuscular injection** in the upper outer quadrant of the buttock. In infants and small children, the midlateral aspect of the thigh may be preferable. When doses are repeated, vary the injection site. Before injecting the dose, aspirate to be sure needle bevel is not in a blood vessel. If blood appears, remove the needle and inject in another site.

Composition: Units benzathine penicillin G (as active ingredient): 2,400,000 units in 4-cc. single dose disposable syringe. Each disposable syringe also contains in aqueous suspension with sodium citrate buffer, as w/v approximately 0.5% lecithin, 0.6% carboxymethylcellulose, 0.6% povidone, 0.1% methylparaben, and 0.01% propylparaben. 300,000 units per cc.—10-cc. multi-dose vial. Each cc. also contains sodium citrate buffer, approximately 6 mg. lecithin, 3 mg. povidone, 1 mg. carboxymethylcellulose, 0.5 mg. sorbitan monopalmitate, 0.5 mg. polyoxyethylene sorbitan monopalmitate, 1.2 mg. methylparaben, and 0.14 mg. propylparaben.

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U.S. Dept. of Health, Education, and Welfare. VD Fact Sheet 1972. Publication No. (HSM) 73-8195.

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Refer to: Baselt RC, Allison DJ, Wright JA, et al: Acute heroin fatalities in San Francisco—Demographic and toxicologic characteristics. West J Med 122:455-458, Jun 1975

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Journal of Medicine

Acute Heroin Fatalities in San Francisco

Demographic and Toxicologic Characteristics

RANDALL C. BASELT, PhD, DONNA J. ALLISON, PhD, JAMES A. WRIGHT, BS, JAMES R. SCANNELL, *and* BOYD G. STEPHENS, MD, *San Francisco*

The mortality rate due to heroin overdosage in San Francisco has increased dramatically since 1968 and now stands as one of the highest in the United States. While the numbers of heroin fatalities in many eastern United States cities have declined substantially in the past few years, the figures for San Francisco and the other West Coast areas continue to increase. The group of heroin overdose victims from the 1970 through 1973 period is more predominantly Caucasian and younger than from the 1963 through 1965 period. In nearly all of the victims, the presence of morphine (a heroin metabolite) was noted in bile or urine, and in about half the results of blood alcohol tests were positive. Measurement of blood morphine concentrations in the victims showed no significant difference from the concentrations noted in a control group of heroin addicts dying from causes other than overdosage.

THERE HAVE BEEN numerous recent reports on the epidemic occurrence of heroin overdose fatalities in the metropolitan areas of the United States during the late 1960's and early 1970's.[1-7] The deaths are generally thought to be directly related to the incidence of intravenous heroin abuse, with the lack of dose standardization of the drug possibly playing a major role.[4] It is apparent from recent statistics that the problem has diminished significantly in many areas of the country in the last few years.[5,6] Law enforcement efforts, addict treatment programs and an increased awareness of the dangers of heroin may have contributed to the decline in the extent of heroin use and the number of fatalities resulting from the drug.

In direct opposition to this picture, however, are the findings in a number of West Coast cities—including San Francisco—which indicate that heroin fatalities are occurring at an ever increasing rate. The purposes of the present study are to describe San Francisco's problem in terms of the population involved and to present the results of forensic chemical examinations as related to the determination of the cause of death.

Methods

In each of the approximately 2,200 cases accepted annually by this office, a complete postmortem examination is given, including a toxicological screening for barbiturates and alcohol and other volatiles. Identification as a heroin overdose fatality is made on the basis of information gathered at the scene of the death and from the pathologic and toxicologic investigations. Gross findings such as hypodermic needle marks or pulmonary edema are used as indicators, while the

From the Office of the Chief Medical Examiner-Coroner, City and County of San Francisco.

Submitted, revised, December 2, 1974.

Reprint requests to: R. C. Baselt, PhD, 850 Bryant St., San Francisco, CA 94103.

presence of morphine (a heroin metabolite) in the blood, bile or urine of the victim is almost always a prerequisite to the decision that the victim died of narcotic poisoning.

The determination of morphine in biological fluids has been done since 1970 with a gas-liquid chromatographic method which is sensitive to as little as 0.05 microgram (μg) per ml of morphine.[8] Hydrolysis in normal hydrochloric acid solution for one hour is done on bile and urine specimens before extraction and thus morphine levels in these fluids represent total morphine content, that is, free morphine plus the pharmacologically inert morphine conjugates. Thin-layer chromatography of extracts of the bile and urine specimens is done to confirm the identification of morphine and to screen for the presence of other narcotic drugs.

Blood alcohol is measured using a gas-liquid chromatographic method which differentiates ethyl alcohol from other common volatiles.[9] Alcohol levels less than 0.02 percent were considered negative.

Results

Heroin fatalities occurred at a more or less regular annual rate in San Francisco until 1966, when the figures began a dramatic increase (Chart 1). Comparative figures for other leading cities in the United States (Table 1) indicate that San Francisco has had in the past few years a very high mortality rate (per 100,000 population) due to heroin overdosage. Based on the first six months of 1974, we expect this city's heroin mortality rate for the year to exceed 11 (per 100,000 people).

Table 2 presents some characteristics of heroin overdose victims from two four-year periods, 1962 through 1965 and 1970 through 1973. While the male to female ratio of the victims is similar to that reported in New York and Washington, D.C., the predominance of whites over blacks in the San Francisco fatalities is in contrast with the figures from these cities.[3,7] Furthermore, Table 2 indicates that the white to black ratio is on the increase, while the average age of the victims has fallen significantly in the last decade. Of the 217 victims included in this study, 160 had known addresses within San Francisco. An additional 40 had no known address, while 15 lived outside of the city and only 2 lived outside California. Figure 1 illustrates the residential pattern of the 160 San Francisco residents within the nine police districts and gives a breakdown of the number of victims within each district. As might be expected, the districts with the highest numbers of heroin fatalities are those with the greatest crime rates and the highest population densities. However, these points of residence do not necessarily represent the areas in which narcotics are purchased or used.

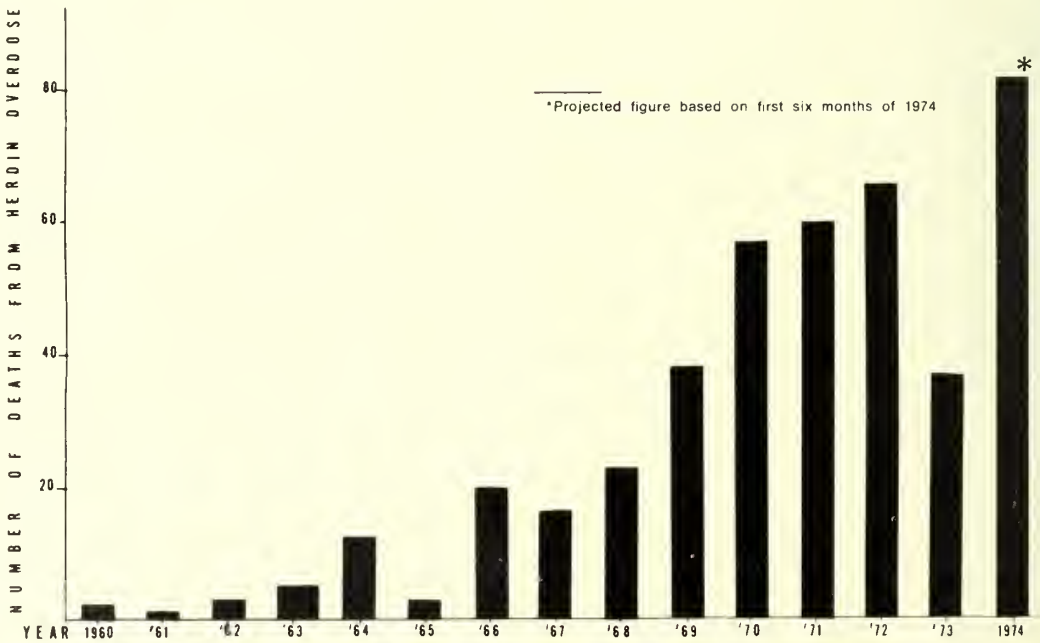

Chart 1.—Heroin overdose victims by year in San Francisco, 1960 through 1974.

TABLE 1.—*Heroin Deaths in Some Leading Population Centers, 1970 Through 1973*

Area	Population	1970 Total	1970 (Rate)	1971 Total	1971 (Rate)	1972 Total	1972 (Rate)	1973 Total	1973 (Rate)
San Francisco	700,000	57	(8.1)	60	(8.6)	66	(9.4)	37	(5.3)
New York City	8,000,000	708[3]	(8.8)	715*	(8.9)	719[10]	(9.0)	372†	(4.7)
District of Columbia	756,000	50[5]	(5.6)	65[5]	(8.6)	38[5]	(5.0)	5[5]	(0.7)
San Diego County	1,400,000	21[11]	(1.5)	24[11]	(1.7)	41[11]	(2.9)	73[11]	(5.2)

*Calculated from figure for first 9 months of 1971.[3]
†Calculated from figure for first 6 months of 1973.[9]

TABLE 2.— *Selected Characteristics of Heroin Victims in San Francisco, 1962 Through 1965 and 1970 Through 1973*

Inclusive Years	Total Deaths	Sex: Male	Sex: Female	Race: White	Race: Black	Race: Other	Average Age	(Range)
1962 - 1965	25	20 (80%)	5 (20%)	12 (48%)	10 (40%)	3 (12%)	38.5	(25-68)
1970 - 1973	217	173 (80%)	44 (20%)	133 (61%)	76 (35%)	8 (4%)	31.5	(15-65)

TABLE 3.—*Toxicologic Tests in Heroin Deaths, 1970 Through 1973*

Total Cases	Morphine Analyses: Blood Tested	Blood Positive	Bile or Urine Tested	Bile or Urine Positive	Ethyl Alcohol Positive	Other Drugs Positive
217	129 (59%)	79 (61%)	209 (96%)	204 (98%)	102 (47%)	61 (28%)

TABLE 4.—*Morphine Levels in Heroin Deaths Not Involving Other Drugs*

Classification	No.	Average Wt. (kg)	Average Morphine Concentrations Plus Standard Error (μg/ml): Blood	Bile	Urine	Average Blood Alcohol (Percent)
Overdose, negative alcohol	27	72	0.43±0.13	32.3±6.1	17.6±4.1	..
Overdose, positive alcohol	36	73	0.42±0.07	12.6±3.3*	13.5±8.7	0.13
Traumatic death, negative alcohol	6	73	0.48±0.18	82.8±33.4†	39.3±10.8	..

*Significantly lower than bile value of the overdose with negative alcohol group ($p<0.01$).
†Significantly higher than bile value of the overdose with positive alcohol group ($p<0.05$).

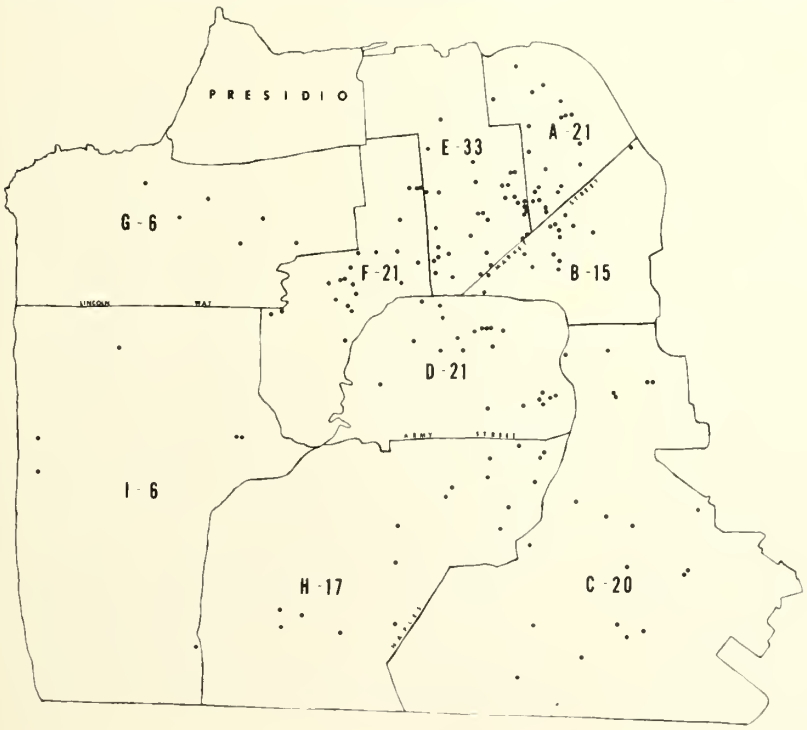

Figure 1.—Residential distribution of heroin overdose victims in San Francisco, 1970 through 1973, by police districts.

Table 3 presents the extent of toxicological testing done on the body fluids of the 217 heroin overdose victims. Bile or urine was analyzed for total morphine content wherever these fluids were available, and a positive result was a primary indicator of a narcotic death. In every case, tests were made for alcohol and other drugs, and the high percentage of positive results in this group is consistent with other similar studies.[3,7]

Blood morphine levels were analyzed as an experimental measure whenever time was available. While less than two thirds of the blood specimens tested were positive for morphine (>0.05 μg per ml), sufficient numbers were obtained to permit an evaluation of morphine concentrations in blood, bile and urine. The averages of these concentrations are presented in Table 4 for three subject groups: overdose victims, overdose victims with positive blood alcohol and a group of heroin addicts dying from traumatic causes. In none of the subjects were significant levels of other drugs besides alcohol found. Average blood levels for the three groups were remarkably similar. The bile and urine values for the overdose victims with alcohol were generally lower than the corresponding values for the overdose victims without alcohol (only the bile average was significantly different), while generally higher bile and urine levels were noted for the traumatic death group.

Comment

It is evident from the results of this study that San Francisco's heroin problem is rising to very significant proportions, and that it is involving an increasingly larger percentage of young white men living in the central sections of the city. While the reasons for this increase in numbers have not become evident, some law enforcement officials have suggested that the extensive efforts of the United States Drug Enforcement Administration to control the supply of heroin to the East Coast have resulted in a diversion of relatively high-grade narcotics to West Coast ports. Although the trend in the past few years has been toward higher concentrations of heroin in drug samples discovered at overdose death scenes, such discoveries are still relatively rare, and not enough of these samples have been analyzed to permit any conclusive statements.

The results of the blood level study indicate that morphine blood levels per se are meaningless in attempting to assign a cause of death in a Medical Examiner's case, since morphine levels found in narcotics users dying of causes other than overdose averaged slightly higher than those of the overdose victims. However, a positive finding for morphine in blood is certainly a further indication of narcotics use and is probably indicative of usage within the four hours before death.[12] Several investigators have shown an inverse relationship between blood morphine levels and the time of survival following heroin administration.[7,12]

Historically, morphine in the bile or urine of suspected overdose victims has only been reported as positive or negative, and attempts at relating the actual concentrations to severity of narcotic effect have usually proven fruitless.[12,13] However, our results (Table 4) show some interesting differences in bile and urine morphine levels. The high levels seen in the group of addicts dying from traumatic causes suggest that these persons had been maintaining a certain level of heroin administration in the recent past, since bile and, to a degree, urine morphine levels represent the end result of the relatively slow processes of liver metabolism and excretion.[12] The lower levels seen in the two overdose groups appear to substantiate the findings of Greene and co-workers[7] that a widespread lack of opiate tolerance was shown in the District of Columbia's overdose deaths. Although this sort of correlation can be made on the basis of the average of a number of cases, it would be impractical to attempt to do it in individual cases because of the great variation seen in individual levels.

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Refer to: McCracken JD: Medical oncology—Clinical experience over one year. West J Med 122:459-463, Jun 1975

Medical Oncology

Clinical Experience Over One Year

JOSEPH D. McCRACKEN, LT COL, MC, *Tacoma*

Over a one-year period, 167 patients with cancer were seen in a total of 1,931 clinic visits. Of these patients, 59 percent responded to therapy, with 20 percent achieving a complete response. The median duration of response was eight months (12+ months for complete responders, 7 months for partial responders), with only a two-month average survival for nonresponders. Seventy-seven deaths in clinic patients occurred for a death rate of 46 percent. Hospital tumor registry referrals rose 46 percent. The effect of early referrals, sources of referral, metastatic sites, chemotherapeutic drugs used, morbidity and type of therapy are also reviewed.

MEDICAL ONCOLOGY is the newest subspecialty in the field of internal medicine. The first subspecialty examination was given by the American Board of Internal Medicine in October 1973. Kennedy and co-workers have outlined the requirements for training of a medical oncologist.[1] However, general physicians, internists and surgeons, have impressed the author as being generally unaware of the capabilities of medical oncologists in clinical practice. Many patients with cancer are not referred to medical oncologists when they have treatable disease that could benefit greatly from chemotherapy, or there is such physician procrastination that, when the patient is referred, he is past the stage when any therapy can be of benefit. The following data were obtained from a comprehensive review of detailed records kept over a year's practice in clinical medical oncology.

From the Oncology Service, Department of Medicine, Madigan Army Medical Center, Tacoma.

Submitted October 9, 1974.

Reprint requests to: Lt. Colonel J. D. McCracken, MC, Box 2558, Madigan Army Medical Center, Tacoma, WA 98431.

Spectrum of Patients Seen and Responses Observed

Over a twelve month period, through the calendar year 1973, 167 patients received some form of chemotherapy or hormonal therapy. The results obtained are shown in Chart 1. Of those patients treated, 59 percent were observed to have responded to therapy. Responses are defined as follows: Complete remission is the disappearance of all evidence of measurable malignant disease with subjective improvement allowing the patient to resume his normal activities. Partial responses are defined as those occurring in patients who achieve greater than a 25 percent reduction in known tumor measurements associated with subjective

improvement. Complete responses were observed in 20 percent of the patients treated. Those patients obtaining complete remission had a median duration of response of 12+ months. Thus, these patients' mean duration of response had not been reached at the time of termination of data for this report (see Chart 1). Partial response was obtained in 39 percent. The median duration of all responders was eight months. Nonresponders to chemotherapy (41 percent) had a median survival time to death of only two months. Therefore, from our experience the majority of patients referred to a medical oncologist will have some benefit from therapy lasting an average of several months.

Although these data were obtained through practice in a military medical center, the majority of patients (81 percent) were retired military personnel or their dependents. Only 19 percent were on active duty or an active duty dependent at the time of their initial referral. More females (51 percent) were seen than males (49 percent). The average age of patients treated was 48.6 years; the youngest treated being one year old, the oldest being eighty-three years of age (Table 1). As most of these patients were in their prime of life, adding several months to these people's lives and returning many of these persons to work, or normal activity, appears of considerable significance.

The most common tumors seen were breast cancer in females and lung cancer in males. The 86 percent response rate in patients with breast cancer was extremely encouraging and is far better than most published reports in the medical literature.[2] The 35 percent response rate of treatment of lung cancer also appears encouraging. However, if one carefully reviews the data listed in Table 2, it is seen that most of the responders with lung cancer were those with oat cell carcinoma, which is the most sensitive of lung neoplasms to chemotherapy. Also, the duration of responses achieved in lung cancer was quite brief, compared to the duration of responses observed in breast cancer. The responses of colon carcinomas, and other tumors listed in the table also appears higher than one would suspect from studies published in the cancer and general medical journals. These studies[2-5] required in most instances a 50 percent reduction in objective measurements of disease to consider a patient as a responder. The author's more generous definition (greater than 25 percent disease reduction) accounts in part for these encouraging response

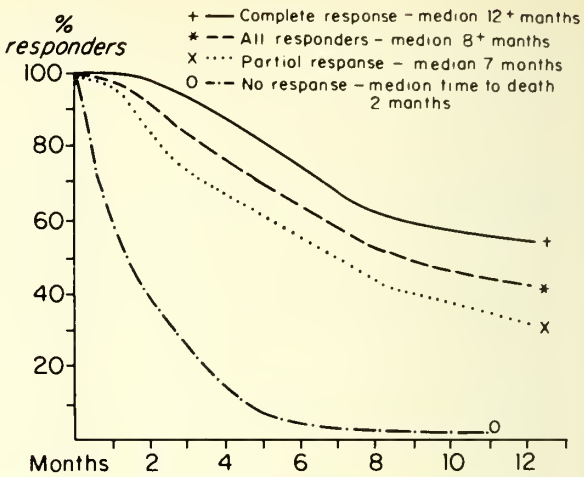

Chart 1.—Percentage of responders and duration of response to chemotherapy or hormonal therapy.

data. Another reason behind this high overall response rate is the early referral of the patient to the medical oncologist for treatment. The majority of patients seen and treated were "good risk" patients referred at the first evidence of disseminated malignancy, before significant cachexia and negative nitrogen balance had ensued. The majority of patients were also seen for the first time as outpatients, rather than as hospital inpatients. Nineteen patients were not treated because they were judged not to be good candidates for chemotherapy, or were seen only on a consultation basis as part of the initial plan for treatment of their malignancy. (For example, nine patients with Hodgkin's disease were seen and staged and found to be candidates for radiation therapy rather than chemotherapy, and referred for such treatment.)

Sources of Referral

Most patients seen at the time of consultation had had some previous form of surgical or radiation therapy or both (see Table 3). The most pa-

TABLE 1.—*Age and Sex Distribution of Patients*

Years	*Males*		*Females*
0-10	2		1
11-20	2		2
21-30	8		5
31-40	6	Median—52 yrs	10
41-50	20	Mean—49 yrs	23
51-60	27		30
61-70	14		11
71-80	1		3
81+	1		1
TOTAL	81(49%)		86(51%)

tients were referred through a radiation therapist. Cooperation among surgeons, radiation therapists and medical oncologists is essential to form an effective cancer treatment team.[6] The disturbing fact is that only 32 of the 167 patients seen had not received previous therapy at the time of their consultation. Attempts to educate general surgeons, general internists and radiation therapists to include medical oncologists in consultation as part of the patients' initial treatment plan improved during the year's time; this resulted in better selection of primary treatment for the cancer patient, as well as close follow-up with early initiation of radiation therapy or chemotherapy at the first evidence of recurrent disease. Tumor boards and joint follow-up clinics with surgeons, radiation therapists and oncologists were held frequently and were often cause for these early referrals.

Metastatic Sites

The areas of metastasis observed in patients at the time of their initial clinic visit are listed in Table 4. Lymph node, liver, lung and bone metastasis were the most frequently seen. Thus, in cancer follow-up clinics, close attention should be paid to these sites as areas for recurrent disease. In most patients seen, more than one metastatic site was noted at the time therapy was begun. Re-

TABLE 2.—*Spectrum of Tumors Seen and Responses Observed*

Primary Site	*Total Patients Seen*	*Patients Treated*	*Complete Response*	*Partial Response*	*Percent Response*	*Alive*	*Dead*
Breast	29	28	6 (11,* 4,* 12, 6,* 12,* 12*)	18 (12,* 9, 12,* 12,* 12,* 5,* 8, 4, 3, 8,* 3,* 8,* 2,* 3,* 12,* 12,* 12,* 11*)	86	22	7
Lung	29	26	0	9	35	7	22
Oat cell	11	10		4 (7, 5, 2, 7)	40	3	9
Squamous, well differentiated	10	8		3 (1.5, 2.5, 3*)	38	3	6
Large cell	3	3		0	0	0	3
Adenocarcinoma	5	5		2 (5, 6)	40	1	4
Colon	15	14	0	5 (7, 4,* 5,* 12,* 4)	36	9	7
Hodgkin's disease	14	5	3 (12,* 12, 12*)	1 (3)	80	11	3
Lymphoma	14	14	6 (12,* 12,* 8,* 12,* 12,* 12*)	7 (11, 12,* 12,* 5, 12,* 7,* 12*)	93	9	5
Head and neck	10	10	1	2	30	5	5
Larynx	2	2	0	0	0	0	2
Oral	5	5	1 (12)	0	20	3	2
Tonsil (squamous)	1	1	0	1 (2*)	100	1	0
Sinus (transitional cell)	2	2	0	1 (8)	50	1	1
Leukemia	14	11	6	2	73	8	6
AML	5	5	2 (12,* 4)	1 (2)	60	1	4
ALL	2	2	2, (7, 7)	0	100	1	1
Diguglielmo's	1	1	0	0	0	0	1
CLL	4	1	0	1 (12*)	100	4	0
CML	2	2	2 (6,* 12*)	0	100	2	0
Multiple myeloma	5	5	3 (12,* 9,* 4*)	2 (12,* 12*)	100	4	1
Melanoma	5	5	1 (6*)	1 (9*)	40	3	2
Unknown primary	5	5	0	4 (12,* 2,* 3,* 12*)	80	4	1
Cervix	5	5	0	3 (4, 8, 6)	60	2	3
Pancreas	4	4	0	0	0	0	4
Sarcoma	3	3	0	2 (2, 10)	67	1	2
Bladder	3	3	0	1 (2.5)	33	0	3
Ovary	3	2	0	0	0	2	1
Stomach	2	2	2 (3,* 2*)	0	100	1	1
Testis	2	2	0	1 (1.5)	50	0	2
Esophagus	1	1	0	0	0	0	1
Thymoma	1	1	1 (12*)	0	100	1	0
Mesothelioma	1	1	0	0	0	1	0
Neuroblastoma	1	0	0	0	0	1	0
TOTALS	167	148	29 (20%)	58	59	90	77

AML = Acute myelogenous leukemia.
ALL = Acute lymphocytic leukemia.
CLL = Chronic lymphocytic leukemia.
CML = Chronic myelogenous leukemia.

*Continuing in response at time of data analysis.

TABLE 3.—*Therapy Before First Oncology Visit*

Type of Therapy	*Number of Patients*
Surgical procedure	34
Radiation	50
Surgical procedure + radiation	40
Chemotherapy	6
Chemotherapy + surgical procedure	1
Chemotherapy + radiation	2
Chemotherapy + surgical procedure + radiation	2
No prior therapy	32

TABLE 4.—*Sites of Metastatic Disease at Initiation of Therapy*

Site	*Number of Patients*	*Responses*
Nodes	54	21
Bone	43	31
Liver	43	20
Pulmonary	41	19
Marrow	18	14
Abdominal	16	6
Central nervous system	12	9
Skin	11	11
Other	6	2
Kidney	2	0
Thyroid	1	1

TABLE 5.—*Chemotherapeutic Agents*

Drugs	*Number of Patients*	*Responses*
5-Flourouracil	68	..
Cyclophosphamide	68	..
Methotrexate	40	..
Vincristine	40	..
Adriamycin	17	..
CCNU	17	..
Bleomycin	12	..
Procarbazine	11	..
Nitrogen mustard	9	..
ICRF-159	9	..
Chlorambucil	8	..
Cytosine arabinoside	7	..
Vinblastine	6	..
Melphelan	5	..
Hydroxyurea	4	..
6-Thioguinine	3	..
Hexamethylmelamine	3	..
Actinomycin-D	2	..
Streptozotocin	2	..
Daunomycin	2	..
5-Azacytidine	1	..
DTIC	1	..
BCNU	1	..
Busulfan	1	..
Mithramycin	1	..
Hormonal agents	46	..
Single drug given or single drugs given in sequence	77	44
Drugs given in combination	71	43

BCNU = 1,3-Bis (2-chloroenthyl)-1-nitrosourea.
CCNU = 1-(2-chloroethyl)-3-cyclohexyl-nitrosourea.
DTIC = 5-(3,3-Dimethyl-1-triazeno)-imidazole-4-carboxamide.
ICRF-159 = (±) 1,2-di(3,5 dioxopiperazin-1-yl) propane.

sponse to therapy did appear to be affected by the metastatic site. Patients with bone metastasis appeared to do quite well, whereas those with nodal metastasis appeared to have a less favorable response rate than associated with other sites. The differences, however, are not of statistical significance. These data indicate that the patient with vital organ involvement can benefit as significantly from chemotherapy as the patient with nonvisceral disease.

Treatments Used and Morbidity

Medical oncology is now in an era of combination chemotherapy. However, most patients treated received single agent chemotherapy, or single agents given in sequence. Those patients receiving combination therapy had no appreciable increase in response rate observed over those receiving single agents given in sequence. The spectrum of chemotherapeutic agents used is listed in Table 5. The four drugs used most frequently were 5-fluorouracil, cyclophosphamide, methotrexate and vincristine. Of significance is that 26 different agents were used, which indicates the large number of agents available to a medical oncologist to treat a patient with disseminated malignancy. Each patient was closely monitored on therapy, with leukocyte and platelet counts obtained before each dosage. Although in many cases significant myelosuppression and thrombocytopenia were observed, by appropriate adjustments in the patient's treatment program morbidity was kept to a minimum. In particular, there were no drug related deaths to infection secondary to drug induced neutropenia, or bleeding secondary to drug induced thrombocytopenia. A drug death is defined as either sepsis due to neutropenia or bleeding due to thrombocytopenia causing death when the patient's disease is under control or not causing serious morbidity. The principal side effects observed, other than bone marrow suppression, were those of alopecia, particularly secondary to cyclophosphamide and adriamycin therapy, and nausea and vomiting, in most cases easily controlled by the use of antiemetics. Therefore, the trained oncologist can, in the majority of patients, administer chemotherapy with minimal morbidity and excellent patient acceptance.

Mortality

Of the 167 patients seen, there were 77 deaths representing a death rate of 46 percent. A medical oncologist could well expect a complete turnover

of his medical practice in a little more than two years. A major role of a medical oncologist is the care of a dying patient and his family. This comprehensive management was greatly appreciated by both patients and their families, and it made it possible for patients to die with dignity and respect without excessive anxiety and fear. Of interest was that 43 percent of deaths in the author's hospital during the year 1973 were due to cancer. This is considerably higher than the national average of 17 percent.[7] It is felt that the explanation for this high death rate from cancer in this institution lies in the fact that a hospital with a full-time radiation therapist and medical oncologist will be a major referral center for a patient with cancer. To support this statement, tumor registry data at our hospital observed in the year 1971, before active radiation therapy and medical oncology services were in use, showed that 235 patients were registered through the hospital tumor registry. In 1973, 343 patients were registered, representing an increase of 46 percent.

Summary

In conclusion, it is felt that a medical oncologist is a valuable addition to any hospital staff with increased referrals of cancer patients expected. The results of chemotherapy discussed in this paper show the current usefulness of chemotherapy in the control of cancer. In the hands of a skilled medical oncologist, toxicities may be kept to a minimum with excellent patient acceptance of therapy. Early referral of the patient with recurrent cancer is paramount in achieving good results with chemotherapy. With the rapid advances being made in this area of cancer treatment, better results and increasing numbers of "cures" will be seen. The ostrich approach to a patient with recurrent cancer should be abandoned forever, and such patients should be referred to the nearest cancer treatment facility with a fully trained medical oncologist, radiation therapist and cancer surgeon for optimum therapy.

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Adoption and Children with Learning and Behavior Problems

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One representative case study is used to illustrate the complex interaction of factors that can lead to tragic family dysfunction when an adopted child has learning and behavior problems. The presence of neurodevelopmental problems in an adopted child, special adoption issues and interparental and intraparental conflicts combine to place the child and his family at high risk. The child's neurodevelopmental difficulties are expressed primarily as subtle learning and behavior problems which make him a focus for parental conflict. In addition, the adoption issues of difference, impermanence, feelings of mutual obligation and fear of abandonment are generally poorly understood and form the basis for the development of unique interactional patterns of communication. Finally, in the families studied, it was often found that the adopting parents had serious personal and/or marital difficulties.

THE PURPOSE of this paper is to review the special and often complicated problems involved in the interrelationship between an adopted child and his adoptive parents. One case, selected from a study of 32 adoptive families in conflict will be discussed in depth. By so doing, the authors will attempt to show, in sharp relief, the complex interplay between neurodevelopmental and emotional-environmental factors which often leads to serious dysfunction observed in adoptive families.[1]

Families with adopted children appear to be at greater risk of serious dysfunction than those with natural children, and, in the authors' experience, such families have been memorable for their tragic dysfunction.[2] In the cases studied, three main factors—often working in combination—contributed to their vulnerability: (1) the presence of neurodevelopmental deviations in the adopted child, on the basis of which learning and behavior problems often ensued; (2) failure by parents to understand and cope with special adoption issues; (3) the presence of serious interparental or intraparental conflict, solutions for which were sought by adoption of a child.

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Discussion

Neurodevelopmental Factors

There is increasing recognition that children with subtle and not so subtle neurodevelopmental problems are more likely than other children to become emotionally unstable, delinquent or schizophrenic when they reach adulthood.[3-6] The exact incidence of neurodevelopmental problems in adopted children is not known.[7] Nonetheless, children who later are adopted often are born of high-risk mothers—those for whom infant morbidity rates are high and who frequently have a

history of obstetrical complications, prematurity, inadequate prenatal care, as well as their own learning and social problems.[8,9] Furthermore, as infants, adopted children frequently have experienced sensory or emotional deprivation and multiple foster home placements before adoption, factors which may lead to, or seriously compound preexisting developmental difficulties.

The developmental problems are generally expressed as subtle specific learning disorders in the presence of normal intelligence, with or without problems of distractibility, impulsivity, incoordination or hyperactivity.[10] The obscure nature of these difficulties leads to an elaborate system of parental denial similar to that found when these same problems exist in a natural child.[11] For example, when parents are told that their child is capable but is not performing adequately in the classroom, they tend to blame themselves or the school, or to seek other simplistic solutions. In many instances, they assume that the child "could" if he "would," imputing unfounded motivational explanations for his underachievement. In some instances, children in such situations may also be given a sense of added power when the parents imply: "You are only doing this to hurt me."

Adoption Issues

The permanent acquisition of an infant or child through adoption introduces a qualitative difference of being *special* or *chosen* to the relationship. At times, awareness of this voluntary selection leaves the child with feelings of difference. Furthermore, an adopted child and his adopting parents share a fear of abandonment and worrisome questions of love and permanence, as well as a mutual burden of obligation. These adoption issues establish the basis for certain unique interactional problems not present in a natural parent-child relationship.

An adopted child, on his part, may feel the need to remain guarded and overly compliant to earn and maintain his position in the family. The parents, in turn, may show concern and oversolicitude to meet their own heavy demands for responsibility and worthiness. In sharp contrast to this self-demeaning, restricted behavior, the child may also harbor worry that he could be *unchosen* and therefore acts out in order to test the permanence of his relationship. As a result, the parents may react to this antisocial behavior with inappropriate acquiescence and thereby establish a model for behavior. When the parents "give in" or "make up" to the child to express their love or handle feelings of insecurity, they are, in effect, teaching the child to feel and say: "If you really love or want me, you will let me have my way." The frequent occurrence of this interaction or "adoption syndrome"[11] *achieves peace at all cost* and by so doing seriously interferes with the child's opportunity to develop optimum frustration tolerance. This is especially true if, on a neurodevelopmental basis, the child frustrates easily, is distractible and has learning problems. Consequently, when adequate frustration tolerance is not achieved from the beginning of the relationship, the parents' ability to set limits with each succeeding stage of parent-child development becomes more and more difficult. The child may ultimately feel empty and worthless, while the parents lack the fulfillment of being parents.

An adopted child also entertains fantasies, pleasant and not so pleasant, about his conception and origins. He may then become intensely preoccupied with a hope of eventually finding his natural parents. This preoccupation can become very threatening to the adoptive parents, especially those most fearful of abandonment. For a few, the fear is so intolerable that knowledge of adoption is withheld and the energy demands placed on the parents to maintain this secret lead to mounting anxiety and stress within the family.

Parental Conflict

There are instances when an adopted child, not unlike a natural child, is expected to fill a void in a parent's life. In others, he may play a part in the myth that "everything will be fine once the adopted baby arrives," the hope that serious underlying marital problems can be resolved. In each case the child is obviously unable to meet this expectation, and by virtue of his difference or learning problems can become a family scapegoat.[12] These factors easily allow the adopted child to become the focus for family conflict by conveniently channeling energy away from personal or marital discord.

The inability to have a natural child can foster a disturbing sense of personal inadequacy, disappointment or resentment. These feelings combined with sorrow concerning the child's adopted state, can often lead to serious parental anxiety and oversolicitude. Furthermore, resentment is intensified when the child is difficult to handle either because of hyperactivity or acting out behavior used to determine the permanence of his relationship.

For some parents, adoption is a way to handle gratitude or assuage guilt by reaching out to someone less fortunate. In so doing, they generally get more than what was bargained for, especially if an asserted effort was made to select an "unadoptable" child—that is, one who is racially mixed or known to be handicapped. Many of these parents are unprepared to meet the demands these special children present in management, and resentment can result from a failure to feel successful. This is particularly true for those parents who must deal with persistent problems, yet still cling to the idea that love and special care should have been the solution for all the child's problems. When the child cannot, for realistic reasons, fulfill parental altruistic or other emotional needs, he may frequently receive the message (spoken or unspoken) that he should feel gratitude toward his adoptive parents ("If it hadn't been for us"). Put in this position, the child is prevented from expressing his feelings, differences of opinion, or even his creative ideas. He can neither gripe nor complain, lest he appear ungrateful for his *good fortune*. As a result, the child may become guarded or "tough," since through such indifference, one can avoid being hurt, or hurting others.

What follows is a case presentation, which demonstrates the way in which many of these complex factors may interact in an adoptive child-parent relationship.

Report of a Case

Tom Smith,* a 15-year-old junior high school student, was adopted at birth, eight years after his mother, age 38, and father, age 50, had given up hope of ever having a baby of their own. Subsequently, they also adopted his sister, Mary, now age 13, and then produced a natural sister, Judy, now age 10. According to Mrs. Smith, little or no information was made available to them at the time of Tom's adoption about the cultural, medical or social background of his biological parents.

At five weeks of life, Tom became severely dehydrated and malnourished before an emergency operation for pyloric stenosis. He developed normally, but from an early age he had difficulty in accepting limits and his parents still have a problem in managing his impulsive hyperactive behavior. He also had a severe deficit in visual-motor integrative function, as well as difficulty in handling cause and effect relationships. Because of delayed acquisition of reading readiness skills, he repeated kindergarten. His continued slow progress in written and spoken language abilities required extra help in summer school for at least four consecutive years.

Mr. Smith, a retired military officer, is a hard working, highly disciplined law enforcement officer with conservative political and social views. He has not spent much time with the family and has been "dynamically absent"[13] while pursuing advanced study and working full time since his retirement. His wife describes him as a secretive man who cannot ask for help and has a mistrust of psychiatry. Mr. Smith was active in athletics as a young man and encourages Tom to participate in Scouting and gymnastics. After nine years, Tom would like to stop his participation in gymnastics; however, he has learned from his father that once he has begun something he would be a quitter if he stopped and would be letting others down who have worked with him. Tom and his father were seen sharing a mutual interest in firearms as they paged through a gun catalogue in the waiting room. Tom has a collection of knives; one of these knives was carried by his father during World War II to be used in case of capture.

Mr. Smith did not accompany Tom and his mother on the first visit. They were seen on an emergency basis after Tom had been suspended from school for using a knife in an unsuccessful attempt to coerce a girl classmate into the bushes. This was preceded by his increasing preoccupation with sexual matters, vulgar behavior, use of extreme language in the classroom and dismissal from summer camp six months earlier for exposing himself. Until this school crisis, Mr. Smith had prevented his wife from seeking private professional help. Tom, however, had been followed in a child guidance clinic for military personnel until seven months earlier, when Mrs. Smith felt he did not need to go in for "chit-chat" with a new therapist who had refused to prescribe medication (which Mrs. Smith felt would help to control Tom's behavior). The working diagnosis was: Unresolved oedipal complex, ostensibly normal intelligence, no neurological dysfunction.

Tom is short for his age. His head is small for his body and he has overdeveloped musculature, in striking contrast to his face and manner which are like that of a younger child. His voice is deepening but has a hollow plaintive tone. He spoke in a stilted manner, using impersonal pronouns as if he were talking about someone else,

*Names used are fictitious.

and appeared haunted and frightened. He held his closely cropped head tilted, as though he were listening for voices, walked in a mechanical manner suggesting a robot or storm trooper, and wore heavy high laced hiking boots with his pants tucked in. Later it was learned that Tom had a long time fascination with Hitler and the Nazi uniform and insignia. Mrs. Smith found this abhorrent, since she is in conflict with her husband over his outspoken social and religious bias. Tom's mechanistic gait and military attire were not seen after the first visit. Furthermore, his guarded stiff manner has gradually disappeared since the onset of therapy and placement in a school program for the educationally handicapped.

At the time of the first interview, Tom stood back from his mother and peered from a half-turned head, avoiding eye contact, though he did make eye contact after the interview proceeded. He blushed and expressed extreme remorse when he talked about exposing himself. Throughout, he tended to moralize and to present a self-righteous impression; he has taken pride in trimming the family lawn because he wants the community to think well of his family.

The school had reported that he had a "dual" personality: one minute he was self-righteous, and the next he was out of control and showed bizarre behavior.

Tom's neurological examination showed an inability to reproduce the human figure. He drew a faceless stick figure with needle-like fingers. He still demonstrates persistent right-left confusion, problems with balance, ambidexterity and poor directional sense. He called the examiner's left hand right, saying that the right hand depends on which way one sits.

The developmental assessment showed a Full Scale Intelligence Quotient of 95 on the Wechsler Intelligence Scale for Children (WISC). The picture was similar to that reported five years previously. At age 10, a school psychologist described him as an atypical child who had problems with ideation, cause and effect relationships, and an inability to formulate ideas in an open-ended situation. He had a verbal veneer which could be mistaken for good intelligence and language skills. Now, although in the 9th grade, he read a 5th grade paragraph with limited comprehension, yet mouthed the words with good phrasing and without error. The isolated skills of spelling, decoding and penmanship were quite good; however, he was unable to integrate them in writing down his own thoughts or in understanding what was read. While he was failing in most of his subjects at school, his parents and teachers were unaware of his serious learning problems. His father, in particular, felt that he functioned quite well at school.

During a conjoint family interview, the aging, conservatively dressed father looked remote and contributed nothing spontaneously. On two occasions he showed extreme anger, which he denied. Tom flushed and looked confused, turned toward the examiner and said, "See! he's angry . . . My mother would get an F for cussing at home and for showing too much feeling, dad doesn't show his at all." During this interview, when Tom expressed anger at his mother, she said with amazement, "I didn't know he ever felt anger toward me." While Tom and his mother do have a close relationship, he has depended upon her to set limits and to make interpretations of cause and effect relationships that he has not been able to handle for himself. It soon became obvious that no one in this family could give a clear message about their feelings.

The glare of Mrs. Smith's glasses covers the expression in her eyes so that her face appears pleasant at all times. The tone of her voice is calm, even when talking about disturbing problems. The father's manner, on the other hand, is usually one of steely silence. When asked how he saw the problem(s) with Tom, he answered abruptly: "I am told that there is a problem and I'm here for *you* to tell *me* what the problem is." While the impressions and findings were being presented, the father let his wife and the examiner do the talking. However, as this discussion drew to a close, he suddenly asked: "How do you arrive at your conclusions?" and "On what basis is this impression made?" (as though he had heard nothing). On terminating the visit, Mr. Smith indicated that he would return only at the examiner's insistence, since his wife was closer to the problems and could handle them alone.

During this same interview, it was learned that Tom thought his mother could read his mind. This idea persists throughout his thinking. It seems that whenever he feels guilty, which is frequently, he knows that his mother is aware of his wrongdoing, and so becomes most uncomfortable with her criticism. She attempted to clarify the issue of such mind reading with Tom, stating: "Yes, I guess I have told you that. What I meant, however, was that when you are so close to someone, you feel that you know what they are thinking."

At that moment, Tom actually expressed relief to learn that someone else could not read his mind in the literal sense. Even so, Tom for the most part continues to feel suspicious about how he is regarded by others.

When Tom was asked to state three wishes, he said first he would like to change the expression on his mother's face because she looked as if she was either judging or criticizing him, and that made him angry; second, that he could have consistent control over himself; and, finally, that he could be less gullible (for instance, every time he got into trouble, someone else led him or made him do it). He referred with anger and resentment to his nonadopted sister, Judy, who he said is a preferred child. Tom has been extremely sensitive about being adopted and special. In fact, he expressed the feeling that adoption has caused all of his problems. No matter how often he has heard genuine statements of love from his family, he is unable to believe them.

Tom tries desperately to please his father to earn his keep, and is extremely fearful of letting him down. He wants to emulate his father, who is a scholar, athlete and law enforcement officer. At the same time, he shares a truly symbiotic relationship with his mother. Differentiation of self has been difficult for both. In addition, his mother blames herself for Tom's problems and has often felt that perhaps another adoptive parent might have done a better job with him. Naturally, she was greatly relieved to hear that part of his difficulties were related to neurodevelopmental factors: "I thought I had taken a perfectly good child and ruined it."

Mr. Smith, on the other hand, tends to deny the existence of any problems. When it was suggested that perhaps Tom would do better in a different kind of school, he insisted that Tom functioned very well, pointing out that he was passed on from year to year. "Besides, if he changed schools he would leave his friends." In reality, Tom is a lonely, isolated child at school. His only social activity is working out at the gym three times a week with children much younger than he. When Tom mentioned that his only skill was gymnastics, his father contradicted him immediately: "You have lots of things going for you; your health, intelligence, good looks, food and lodging."

Discussion of Case

The case up to this point illustrates the way in which subtle neurodevelopmental problems combined with special family dynamics contributed to Tom's difficulties. Tom's limited and literal interpretation of cause-effect relationships, poor impulse control, persistent right-left confusion, inability to integrate isolated written and spoken language skills and, therefore, failure to fully understand what is read, have prevented him from experiencing the world about him as others do. On the other hand, his father's denial of the real learning and behavior complications places unrealistic expectations on Tom which he meets with inappropriate acquiescence. Since his real problems and feelings are unrecognized, his hidden anger is expressed in fantasy. He projects his anger to the world about him, mainly against his mother and nonadopted sister, by assuming the role of a strong Nazi who can rid the world of inferiors (like himself). For example, when instructed to check with his mother as to whether she were angry with him, she answered: "I love you more than anyone in the family . . . you mean more to me than all the others . . . and look at those beautiful blue eyes."

In what way does Tom's being adopted play into the dynamic process leading to his decompensation and dysfunction? In this particular kind of family many of the difficulties could have occurred even if Tom had been a natural child. What has not been discussed is the mother's description of her emotional divorce[14] from her husband, as illustrated when she said, "The reason I wanted a child is because I knew my husband didn't love me. My life had no meaning before Tom came into my life; Tom made me feel loved and worthwhile." Her close association with her adopted son and their failure to develop boundaries and differentiation from one another, developed into a symbiotic relationship.

Also, Tom has never quite become reconciled to the idea that he is adopted. He feels different and impermanent. He *is* different from his parents and nonadopted sister not only because of significant learning problems, but also because being adopted makes him feel apart from the rest. At one point he said he would like to "knock off" Judy, the parents' natural child, and that sometimes he is so angry with his mother he wants to take a machine gun and "blow her head off . . . " He asked, "How is it possible that mother says she loves me more than the rest when she's angry with me all the time?" Mrs. Smith denied being angry with Tom all of the time and told him, "I get angry with you, then I'm over it." Tom never

stops to check out his mother's feelings and projects his own anger on to her, assuming that she is angry with him all the time. He said, "I wish Judy were adopted." He also discussed his pressing wish to find his natural parents, so that he could be united with them. Mrs. Smith promised him that when he is 21 he can search the records in the courthouse of the county where he was born for the names of his natural parents.

Tom has never felt a sense of permanence; it is as though he is biding his time. On the one hand, he wants to emulate his adopted father's goals and values and, on the other, says emphatically that he doesn't want to be a Smith and feels burdened with the demands and feelings of obligation placed on him by their adoption. No matter how much he is told by his mother that he is loved, he is unable to accept or believe this. Because he cannot trust himself, he cannot trust others and the anger he feels toward his mother and her natural child he thinks is projected toward him by them. He does not like the way each of them stares at him; "it is different with Mary" (his adopted sister), with whom he feels an alliance.

When he experiences his violent feelings toward his mother, Judy, and to his father, he is told "all children feel this way." Tom said, "I hope I can control myself, I don't want to hurt anyone." When he shows painful anguish in his facial expression, his mother neither sees nor comments on this. The duality and conflict of good and evil are summed up by the mother, when she says, "There are two Toms that leave the house in the morning." The father's failure to acknowledge the seriousness of the problem is made more poignant by the mother's comment that "Dad talks to the children about their grades (using proverbs or adages) but never talks to the real children."

After the evaluation of Tom and his initial treatment, Mary, his 13 year old adopted sister, ran away from home and was flown home by juvenile authorities after being found a thousand miles away. During her absence, Mrs. Smith was left alone to handle her anguish while Tom and his father went on an outing with the Scouts. Mrs. Smith began to cry with hopeless despair. She said, "This has been the worst day I have ever spent in my life . . . Chuck (Mr. Smith) has never loved me; he may respect me but there has never been any love."

Mrs. Smith is critical of Mary's handsome boyfriend whom she said ". . . will probably lay her out flat in the park and get her pregnant." Tom became very angry with his mother as she spoke. He felt that this information should be kept secret, but said, "I would never run away." Even so, Tom questions his permanence.

Many of the problems that developed in this case (such as Tom's escape from the family by becoming psychotic and Mary's abrupt separation from the family by running away)[14] can be explained in part by the presence of the binding quality of the family dynamics. Tom's literal and simple interpretation of cause and effect relationships constantly places him at an impasse. If he is loved, then how can his mother become angry with him, if he is burdened with an obligation to be dutiful and thankful for his adoption, how can he express his own feelings and needs? It is unthinkable for him to ask his father if he can stop going to the gym or allow his hair to grow. Tom's strong either-or feelings and inappropriate acquiescence to unrealistic internal and external demands have led to his psychosis, a way in which he could separate from himself, his mother and family.

Mrs. Smith is a naive loving person, who does not quite believe what she sees, or quite see what she believes and is threatened when her children do not share her ideas and value system. Whereas Mr. Smith seems to hear and see what he wants to believe, is secretive, remote and noncommunicative, and greatly mistrusts the world about him.

Mary, like her mother, experienced her father's isolation as indifference. On the other hand, she is in conflict with her mother about such things as the way she dresses and her choice of friends. Before her recent thrust of adolescent assertion, Mary was appreciated for her independence and affectionate nature. She had assumed more than her share of household responsibilities and, in fact, had been reluctant to express her individuality. Now, however, both parents regard her as manipulative and do not trust her even when she is loving. Mary stated that she ran away from home to experience freedom, yet felt sad about hurting her mother. Her mother's response was: "If you run away again, don't bother to come home . . . unless of course, you get pregnant."

During Mary's absence, Mrs. Smith found her diary. The entries were signed with her biological surname. To her mother, this was "the last straw." She said that she had reached the point of giving up with the children and wanted to wash her hands of everything. Although Mary responded to this

message of disillusionment and despair with tears, and made attempts to comfort her, her mother merely turned her head and remained unyielding.

Because Mary now shared the role with her brother of an *identified patient* in this family, it was felt that an evaluation of her educational and developmental status might enhance understanding of the dilemmas she too confronted vis-a-vis parental expectations. Fortunately, her mother had kept a careful record of Mary's progress and social adjustment in the early grades. It seems that she had had serious difficulties learning to read; her third grade teacher had described her as "impatient with learning concepts," yet a jovial, good natured youngster. (The mother now feels that Mary's bubbly, "cheery-bird" moods are contrived and merely precede a request for a favor.)

Results of individual achievement and intelligence batteries (Wide Range Achievement Test, Durrell Analysis of Reading Disability and Wechsler Intelligence Scale for Children—R) were of interest in several respects. First of all, significant lags were observed between level of grade placement and performance not only in reading but in spelling and arithmetic as well. Second, while Mary's aggregate intelligence score fell well within the range of "average-normal" (Full Scale I.Q.—103), she had mild, yet consistent difficulty with tasks relying upon abstract-conceptual reasoning.

The deviations in Mary's thinking patterns and scholastic accomplishments were, of course, far less striking than Tom's. Nevertheless, the family had always assumed that she was a highly capable youngster. Their belief that her frequent truancy, and her problems coping with academic demands, resulted solely from poor motivation or boredom had only added to their resentment. From the mother's viewpoint, the runaway episodes (there had been others), the class cutting and the lagging achievement in school all represented instances of how Mary had "let her down."

Mary felt trapped. School was boring and she had had restrictions placed on her that were more appropriate for a younger, more compliant child. During most of the sessions Mary appeared sullen and without hope. Occasionally, she smirked or laughed sarcastically, probably showing remnants of her former cheery defensiveness.

Just before this writing, there was an interesting development in the case. Mrs. Smith came for her therapy hour appearing far less depressed, if not rather chipper and optimistic. It seems that Mary's difficulties were beginning to have the effect of bringing her and Chuck (Mr. Smith) closer than they had been for years. With an expression of delight, she went on to say that they were now forced to share the burden, and to solve problems together. Blushing, she remarked, "It could even develop into a new romance . . . but I won't allow myself to be hurt again." (The mothers' den and bedroom are on the basement level where Tom sleeps, while the father's sleeping quarters are on the third floor with the girls.) While it is still too early to foresee the final outcome, there has been some progress. There has been an acceptance by both parents of the children's real, though rather obscure, learning problems. Tom's behavior has become more appropriate and socially acceptable. For the most part he seems more comfortable, and he states that he has become less suspicious of others' motives. Mr. Smith has taken full charge of handling Mary. She is permitted to stay out later and to date an older boy in the neighborhood.

Conclusion

One case is reported which illustrates an adoptive family in crisis and is representative of some of the issues involved in 32 of the adoptive families studied in which the identified patient was an adopted child with learning and behavior problems. In addition to the failure to cope with the adoption issues and the presence of interparental and intraparental conflict, the child's subtle neurodevelopmental differences influenced his learning and behavior.

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Cystic Fibrosis Complicated by Heart Failure

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Survival studies were done on 36 children with cystic fibrosis and heart failure. Thirty percent did not survive the first four weeks, and the median survival for the group was between two and three months. By the end of the first year from the onset of failure, 74 percent had died and at 30 months, 87 percent had died.

COR PULMONALE with heart failure has long been recognized as an important cause of death in cystic fibrosis.[1,2] This complication, always ominous, is generally considered a terminal or near terminal event. However, in rare instances the cardiac process can be successfully reversed, and the patient may survive for an indefinite period.[3]

This investigation was undertaken to determine the temporal relationship of heart failure and death in cystic fibrosis with the hope that this information would prove useful from a prognostic standpoint.

Material and Methods

A total of 36 patients were studied (Table 1). There were 20 females and 16 males, and the age range was from six months to 26 years. All had cystic fibrosis previously confirmed by sweat chloride tests. In all, the disease process was very severe (Shwachman-Kulczycki clinical score[4] less than 40), for a period of six months to five years. There was overt evidence of heart failure in 31 patients as evidenced by either hepatomegaly, cardiomegaly or edema in addition to extreme respiratory distress. Since findings on blood gas tests and electrocardiograms were consistent with advanced cor pulmonale[5] in the remaining five patients, they too were presumed to have some degree of heart failure. Teleroentogenograms were taken in each subject and were read in a blind fashion; the interpreter being aware only that the patient had cystic fibrosis. The same was true of the electrocardiograms. Pulmonary function tests were done whenever the age and clinical condition of the patient permitted.

In each case, the illness appeared terminal. Respiratory insufficiency became more severe and was assumed to be due to intercurrent pulmonary infection. This was probably the precipitating cause of heart failure. Cyanosis, tachycardia, dyspnea and orthopnea were constant features. Hepatomegaly was present in 17; cardiomegaly in 26; and edema in 19. Arterial oxygen partial pressure (PaO_2) was measured in 25 patients and was less than 50 mm of mercury in 23. Arterial

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TABLE 1.—*Pertinent Data in 36 Patients with Cystic Fibrosis and Heart Failure*

Patient and Sex	*Age (Yr.)*	*Current Status*	*Hepato-megaly*	*Edema*	*Cardio-megaly (x-ray)*	*ECG*	*(VC) (percent)*	*PaO_2 (mm.Hg)*	*$PaCO_2$ (mm.Hg)*	*PH*
1 .. ♂	25	died at 5 mos.	+	+	+	RVH, RAD	..	51	56.5	7.42
2 .. ♀	12	died at 19 days	+	−	−	RAD	..	48.5	34.5	7.50
3 .. ♀	7	died at 1½ mos.	+	+	+	RVH, RAD	..	33	65	7.42
4 .. ♀	24	died at 1½ mos.	−	+	−	RVH, RAD	..	48	39	7.44
5 .. ♀	16	died at 2 mos.	+	+	+	RVH, RAD	..	41	55	7.48
6 .. ♂	8	alive 14 mos.	−	−	−	RVH, RAD	37	36	47	7.35
7 .. ♂	16	died at 3 days	−	−	+	RVH, RAD	..	33	34	7.46
8 .. ♀	18	died at 2 mos.	+	+	+	RAD	..	34	63	7.37
9 .. ♂	24	alive 9 mos.	+	+	+	RVH, RAD	..	30	80	7.46
10 .. ♀	4	died at 9 mos.	−	−	−	RAD	..	56	48	7.36
11 .. ♀	22	alive 4 mos.	+	−	+	RVH, RAD	..	45	52	7.40
12 .. ♀	3	died at 5 mos.	+	+	+	RVH, RAD	..	27	61.5	7.27
13 .. ♀	½	alive 26 mos.	+	+	+	RVH, RAD	..	39	78	7.21
14 .. ♂	20	died at 14 mos.	+	+	+	RAD	44	..	..	..
15 .. ♂	18	died at 2 days	−	−	+	RAD	29	..	..	..
16 .. ♀	8	died at 6 mos.	−	+	+	RVH, RAD	..	..	..	..
17 .. ♂	7	died at 6 mos.	−	+	+	RVH, RAD	..	..	..	..
18 .. ♂	5	died at 3 days	−	−	+	RAD	..	48	..	..
19 .. ♀	15	died at 1 mo.	−	−	+	RVH, RAD	27	..	..	..
20 .. ♂	3	died at 24 mos.	+	+	+	RVH, RAD	..	..	..	..
21 .. ♀	19	died at 1 mo.	−	+	+	RVH, RAD	..	41	68	..
22 .. ♀	26	died at 44 mos.	+	+	+	RVH, RAD	..	..	..	..
23 .. ♂	15	died at 4 mos.	−	+	+	RVH, RAD	..	35	56	..
24 .. ♀	14	died at 34 mos.	−	−	+	RVH, RAD	..	..	..	..
25 .. ♀	10	died at 2 mos.	−	−	+	..	..	20	55	..
26 .. ♂	17	died at 24 mos.	−	−	−	..	32	42	50	..
27 .. ♀	13	died at 6 days	−	−	+	RAD	29	34	42	..
28 .. ♂	7	died at 24 mos.	+	+	−	RVH	..	..	..	..
29 .. ♀	12	died at 10 days	..	..	+	..	33	28	67	..
30 .. ♀	1	died at 11 days	−	+	−	RVH	..	..	..	..
31 .. ♀	15	died at 11 mos.	−	−	−	RVH, RAD	30	54	29	..
32 .. ♂	5	died at 24 mos.	+	+	+	..	..	..	..	..
33 .. ♂	15	died at 13 mos.	+	−	+	RVH, RAD	18	18	54	..
34 .. ♀	10	died at 2 mos.	+	−	−	RVH, RAD	44	41	50	..
35 .. ♂	3	alive 60 mos.	+	+	+	..	..	18	73	..
36 .. ♂	13	alive 62 mos.	−	−	−	RAD	60	45	46	..

ECG = electrocardiogram
VC = percent of predicted vital capacity
RAD = right axis deviation
RVH = right ventricular hypertrophy
PaO_2 = arterial oxygen partial pressure
$PaCO_2$ = arterial oxygen carbon dioxide pressure

carbon dioxide partial pressure ($PaCO_2$) was greater than 45 mm of mercury in 19 of the 24 patients in whom it was measured. These values have been previously shown to indicate severe cor pulmonale.[5]

Therapy consisted of oxygen, mist, antibiotics, digoxin and supportive measures. Digoxin was administered in full dosage.[6] Initial digitalization was carried out over a 24 hour period following which maintenance therapy was begun. No evidence of digitalis toxicity was observed.

A survival curve was constructed using the methods suggested by Cutler and Ederer.[7] For this purpose, the date of documentation of heart failure was considered the date of onset. Cumulative survival was calculated for each month thereafter until conclusion of the study on October 1, 1973.

Results

The results are presented in Figure 1. As illustrated, 30 percent of the patients were never discharged from the hospital, since they did not survive the first four weeks. Median survival for the group was between two and three months. Thereafter, the decline in the number of survivors was at a more gradual rate. By the end of the first year, 74 percent had died and at 30 months, 87 percent had died.

Of the six patients still alive, all are at home

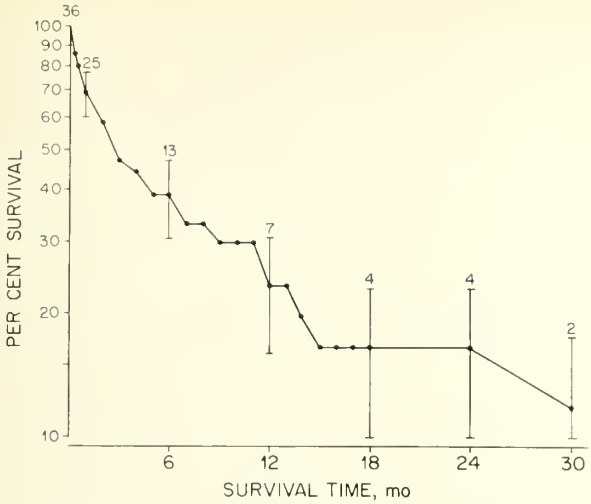

Figure 1.—Survival of cystic fibrosis patients complicated by cor pulmonale with heart failure. Date of onset was taken as date of documentation of heart failure. Standard error is displayed at six month intervals. Numbers on graph give number of patients surviving beyond indicated survival period. Method of calculation was that of Cutler and Ederer.[7]

and there has been no recurrence of heart failure in any of them. Four were of school age and two of these are attending school regularly. All six continue to take digoxin and two require oxygen therapy intermittently. The two patients who have survived longest are now more than five years beyond their episode of heart failure.

Discussion

The results of this study indicate that the cardiac process may be reversed in the majority of patients with cystic fibrosis in whom heart failure occurs. It is not necessarily a terminal event, and over two thirds of such patients can be expected to improve to the point where they can be discharged from the hospital. A significant proportion return to their previous functional status and survive for more than a year.

It is suggested that vigorous therapy is justified in patients with cystic fibrosis in whom congestive heart failure develops. Because management in this study was comprehensive—including respiratory care, vigorous antibiotic therapy and digoxin—it is not possible to identify which component contributed most to survival.

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Medical PROGRESS

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Iron Nutrition

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IN VIEW OF the abundance of iron on this planet, it is not surprising that this metal would be chosen for the critical function of oxygen transport. Elaborate systems regulating iron exchange with the environment and the transport of iron within the body have evolved. While these appear quite adequate for most animal species, there is reason to question their effectiveness in man. World-wide, iron lack is the commonest deficiency state encountered. In large segments of the population both the amount and availability of ingested iron is insufficient to replace the small quantities of iron normally lost. This review will attempt to clarify the nature of external iron exchange between man and his environment. Attention will be focused on the population at large rather than on pathologic mechanisms affecting iron metabolism.

Iron Balance in Humans

Functional or essential body iron contained in circulating hemoglobin, myoglobin and intracellular iron-containing enzymes represents about 35 mg of iron per kg of body weight. Beyond this there is a variable quantity of storage iron which serves as a buffer against sudden losses due to bleeding or for the needs of pregnancy. In adult men storage iron represents about 15 mg per kg of body weight or one third of total body iron, whereas in women storage iron varies widely between 0 and 20 percent of total body iron.

Daily requirements for iron are dictated by a small and constant obligatory loss from the body. In a normal 70 kg (154 pound) man this averages about 10 percent of body iron per year or about 0.9 mg per day.[1] Two thirds of this loss occurs via the gastrointestinal tract of which roughly one half or 0.4 mg is due to extravasated red blood cells.[1] Additional small losses occur via the skin and urinary tract. While total losses vary somewhat in relation to the amount of body iron, the limits of such compensation are narrow, from perhaps 0.5 mg with severe iron deficiency to 2 mg with iron overload.[1-3]

In normal women substantial additional losses of iron occur as a result of menstruation. Studies in different geographic areas have yielded surprisingly similar values for menstrual loss which amount to about 40 ml of blood each month or a daily loss of 0.5 mg of iron.[4-6] The distribution of this menstrual loss within a population is highly skewed and 5 percent of women have losses of more than three times this amount.[4] Additional iron losses occur in women during pregnancy due to the needs of the growing fetus and placenta. The net cost of pregnancy is 500 to 700 mg of iron.[7-10] Growth in infancy through adolescence also imposes increased iron needs.

To balance these physiologic requirements a constant influx of iron from the diet is required.

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The amount of dietary iron is closely tied with caloric intake, and the iron to calorie ratio (6 mg per 1,000 kilocalories) varies remarkably little in different economic segments of the population.[11] In adult men with an average intake of about 2,500 kilocalories and an iron intake of 15 mg per day, only 6 percent of ingested iron need be absorbed to maintain iron balance. Stores of ferritin and hemosiderin in normal man average about 1,000 mg, sufficient iron to replace normal losses for three years if absorption were to be completely abolished. Therefore the appearance of iron deficiency in man almost always signifies an excessive iron loss, usually due to bleeding from the gastrointestinal tract. In addition, a man on a typical American diet can maintain body iron in the face of loss as high as 2.0 to 3.0 mg of iron or 16 to 20 percent of dietary intake.[10] Iron balance in menstruating women is much more precarious. Dietary iron intake amounts to about 11 mg per day so that with average requirements of about 1.3 mg per day, 12 percent of ingested iron must be absorbed to maintain balance. Average stores in menstruating women amount to about 300 mg or about one third of the level in men.[12-14] These stores are considerably less than the demands of a normal pregnancy, a fact that explains the very common occurrence of iron deficiency during pregnancy if additional iron is not given.[8,10,15-18] From these general studies of iron balance it is apparent that there is a limited capacity of absorption to meet increased requirements in those segments of the population with special needs. Some of the reasons for this have only recently been clarified through studies of iron absorption.

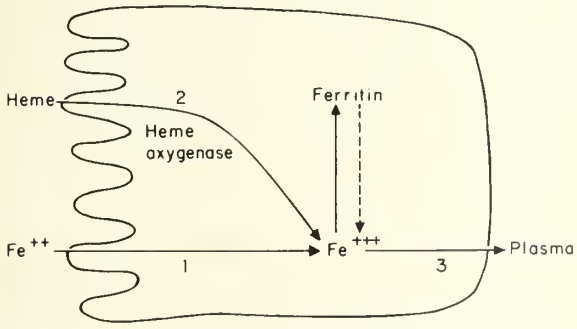

Figure 1.—Iron transport by the intestinal mucosal cell. There are two pathways by which iron from the lumen of the gastrointestinal tract can enter the mucosal cell. The major pathway is in the form of reduced ionic iron (1) which represents the largest portion of ingested dietary iron. Iron can also enter the mucosal cell as an intact porphyrin complex (2) which is degraded within the cell by heme oxygenase with release of iron to the intracellular pool. From the latter, iron is either transported to the serosal surface when it enters the circulation (3) or is incorporated into ferritin as storage iron (4). Although a portion of this storage iron may be available for later transport into the body (interrupted line) most of this iron is lost from the body when the mucosal cell is sloughed at the end of its 4 to 5 day life span.

The Absorptive Mechanism

The interface between ingested iron and body iron resides in the mucosal cell of the upper small intestine. By controlling entry of iron into the body, the intestinal mucosa determines the amount of total body iron. There are two chemical forms of iron which enter the mucosal cell from the intestinal lumen (Figure 1). One of these is ionic iron, assumed to be largely reduced iron due to its greater solubility.[19] This ionic iron is initially bound to the brush border before being transferred into the mucosal cell.[20] This portal of entry is not specific for iron but is apparently shared by and can be competitively inhibited by a variety of heavy metals including cobalt, manganese and zinc—but not copper or magnesium.[21-24] The other absorbable form of iron is as a porphyrin complex derived from hemoglobin and myoglobin.[25-28] Once within the mucosal cell, this heme iron is enzymatically degraded and the released iron enters the ionic pool of mucosal iron.[27,29,30]

Following entry into the mucosal cell there are two major pathways of iron transfer. A portion of newly absorbed iron is rapidly transported to the serosal side of the cell where it gains entry into circulation. This rapid phase of iron transport is undoubtedly mediated by a specific carrier protein[31-36] and recent studies have provided some evidence that this may be transferrin.[37] The alternate pathway for iron is its incorporation into ferritin. Despite much recent study of intracellular transport of iron by the mucosal cell, the biochemical events of this process are still poorly understood. Whereas earlier studies suggested that ferritin was intimately involved with iron transport by the mucosal cell into the body, iron enters this fraction only after the rapid phase of iron transport is largely completed. Incorporation of absorbed iron into ferritin, therefore, appears to be a passive phenomenon for the storage of iron which has not been transported out of the cell.[38] Although a portion of ferritin iron may later be transferred into the body, most iron in this form

is lost from the body with exfoliation of the mucosal cells.[39-42]

Mucosal Regulation

Regulation of iron absorption by the intestinal mucosa functions so as to maintain an adequate complement of body iron. Experimentally, a large number of factors have been shown to modify iron absorption, the most important of which include body iron stores,[43-46] the rate of erythropoiesis,[43,47-49] and hypoxia.[50-53] In human subjects without disorders in intestinal absorption or internal iron metabolism, the main determinant of iron absorption is the level of body iron stores.[3,54-56] Absorption is enhanced not only with frank iron deficiency anemia but also in latent iron deficiency where a reduction in iron stores has not yet affected the level of plasma iron. Thus, blood donors with no evidence of iron deficient erythropoiesis absorb iron at a level twice that of nondonors,[46] and women with their lesser iron stores absorb iron at a rate twice that of normal men.[57] During pregnancy a progressive rise in iron absorption is observed as iron stores become gradually depleted.[54] Conversely, enlargement of iron stores by parenteral iron administration results in decreased iron absorption.[44]

Despite an intensive search for a mechanism by which these alterations exert their influence on the mucosa, a specific humoral regulator which could account for all experimental observations has not yet been identified. A hypothesis to account for this reciprocality between iron stores and iron absorption was advanced by Crosby and coworkers.[39-42,58-61] It was proposed that iron supplied from the plasma to the mucosal cells during their formation in the crypts of Lieberkühn conditioned the cell for its subsequent handling of luminal iron. In persons with lower iron stores less iron would be supplied to the mucosal cell which would then transport increased amounts of luminal iron during the four to five day cell life span. A higher supply of body iron would have a reciprocal effect. Despite many attractive aspects of this hypothesis it does not explain the signal from iron stores to the mucosa which operates in persons with normal hemoglobin, normal plasma iron, normal transferrin saturation and normal plasma iron turnover.

Luminal Factors

For the intestinal mucosa to perform its function in regulating iron stores, there must be sufficient quantities of luminal iron in a form which can be assimilated. Factors within the gastrointestinal tract which influence the assimilation of nonheme iron are to some extent predictable on the basis of the physiochemical properties of the metal. The limitation of iron absorption to the upper part of the small intestine is undoubtedly explained by the increase in pH below this region of the gut which precipitates ferric iron as an insoluble macromolecular complex. Several studies have shown that persons with achlorhydria absorb iron less well, indicating some importance of gastric secretion.[62-66] It has also been suggested that another constituent of gastric juice facilitates absorption by forming small molecular complexes with iron which remains soluble at a pH above 5.[67] Conversely, a high molecular weight iron-binding substance in gastric juice, called gastroferrin, has been described and was believed to prevent iron absorption.[68-70] Later studies, however, have not confirmed the importance of gastroferrin as a regulator of iron absorption.[71,72] Experimentally, a reduction in pancreatic secretion has been shown in animals to enhance iron absorption[73-75] and in humans, chronic pancreatitis has been proposed as a cause of excessive accumulation of body iron.[76-80] Recent workers have doubted the importance of pancreatic secretion in disorders in iron balance.[81-83] In summary, despite a number of reports proposing otherwise, luminal factors other than pH have not been yet established as important in iron absorption. The only clinical abnormality in the luminal phase of iron absorption which frequently leads to iron deficiency is partial gastrectomy, where a disturbance in gastrointestinal motility even more than gastric secretion appears to be responsible.[84-88]

Dietary Factors

In human iron nutrition, the most important considerations are the amount of iron and type of diet in which it is ingested. While the amount of dietary iron has long been a matter of concern, its limited availability has been obscured by extrapolating data obtained in small laboratory animals to man. Rats for example have been used extensively in studies of human iron nutrition. However, the capability of rats for iron absorption is quite different from that of humans: nonheme iron is much better absorbed than in humans, but heme iron less well.[27]

In recent years, extensive isotopic measurements of food iron absorption have been made in

humans, which make extrapolation from animal studies unnecessary. The problem with isotopic measurements of food iron availability in humans has been the great variation in measurements.[46,89] A large portion of this variation is due to differences in absorption within the same person when tested on different days. This day-to-day variation can be reduced by partitioning the test dose over several days[90] and by including a sufficient number of subjects in each study to obtain statistically meaningful data. The remaining component of variability is due to differences between persons studied, which in turn reflect differences in their level of iron stores. This type of variation can be circumvented by doing multiple absorption studies in the same person using two radioiron tracers.[46,90] Since iron status varies appreciably in different geographic regions of the world, absorption tests should always include a standard reference dose of inorganic iron.[91] By expressing absorption of food iron relative to this reference dose rather than as an absolute measurement, studies performed in subject groups of widely different iron status can be compared.

Initial efforts to understand food iron absorption employed single food items which had been biosynthetically labeled as first described by Moore and Dubach.[92] This was accomplished by growing vegetal foods in hydroponic media tagged with radioiron and by injecting radioiron intravenously into animals several months before they are killed. Data obtained by these techniques have been reviewed.[93-95] The most important finding in such studies was the much lower availability of vegetal sources of iron as compared with animal tissues. For the former, mean absorption ranged from a low of 1 to 2 percent from rice and spinach to a high of 6 to 7 percent from soybeans. Absorption from maize, black beans and wheat—which are all staple food items in various areas of the world—had intermediate levels of absorption of 3 to 4 percent with a ceiling in iron deficient subjects of about 10 percent. Absorption from animal sources which have included beef, fish and liver were at substantially higher levels of 15 to 30 percent and approached the absorption rates of comparable doses of ferrous sulfate. The limitation of such single-item absorption studies became apparent when two foods were administered simultaneously, each of which has been biosynthetically tagged with separate isotopes of iron. For example, when fish is administered with maize, absorption of the former is decreased to about a half while the latter is nearly doubled.[96] In view of the complexities of a modern diet, studies with biosynthetically tagged foods have limited application to the evaluation of food iron nutrition. Unless a way was found to evaluate iron absorption from a complete meal, absorption data would have little meaning.

The measurement of food iron absorption has recently been shown to be possible in a different manner. The technique is based on the extrinsic radioactive tagging of dietary heme and nonheme iron. It was initially observed that when a small quantity of inorganic iron was mixed with a vegetal food at the time of administration, absorption of this extrinsic tag was nearly identical with that of the biosynthetic or intrinsic radioiron tag.[97] This observation has been validated now for a large number of vegetal foods and in several laboratories.[98-103] An important extension of these findings was the demonstration that if an homogenized meal containing several vegetal foods was tagged extrinsically, absorption of the extrinsic tag was nearly identical to any one of the food items which had been intrinsically labeled.[97] This provided convincing evidence that for foods ingested simultaneously, a common pool of absorbable nonheme iron is formed, the absorption of which could be measured with an extrinsic tag. The same principle could be employed to measure absorption of dietary heme iron by adding a small amount of radioactive hemoglobin to the meal.

By adding different radioisotopes of iron to separately label the heme and nonheme iron pools, total iron absorption from a complete meal could be determined.[103-107] The two pool extrinsic tag method has yielded measurements of food iron absorption which agree closely with estimates based on normal body iron loss. For example, meals composed of aliquots of all foods consumed in a typical six weeks' diet and doubly tagged with radioactive heme and nonheme iron were administered to 32 young men.[107] The total daily intake of iron in these men was 17.4 mg, of which only 1 mg was in the form of heme iron. Total absorption averaged 1.25 mg per day. Absorption of nonheme iron averaged 5.3 percent or 0.88 mg per day whereas absorption of heme iron averaged 37 percent or 0.37 mg of iron. Similar data have been obtained by Martinez-Torres and Layrisse[104] who employed a meal of meat, black beans, maize and rice containing a total of 4.5 mg of iron. In normal persons, absorption from 1.5 mg of heme iron was 27 percent or 0.34 mg as compared with

an absorption from 3.0 mg of nonheme iron of 6 percent or 0.12 mg. Total absorption from the meal was, therefore, 0.46 mg of iron. In iron deficient persons, absorption from heme and nonheme iron increased to 37 percent (0.52 mg) and 14 percent (0.43 mg) respectively to give a total iron absorption from the meal of 0.95 mg. These studies indicate that when meat is consumed regularly in the diet, relatively small amounts of heme iron may account for a sizable portion of food iron absorption. Unfortunately, the intake of heme iron in an appreciable portion of the world population is negligible.

Evidence that the absorption from the nonheme pool may be notably influenced by the composition of the diet has focused attention on those substances within the diet which affect availability. Ascorbic acid is a potent enhancer of iron absorption, not only because of its ability to reduce iron but also by forming a chelate with ferric iron at low pH which remains soluable at the higher pH of the duodenum. Recent studies have shown an enhancing effect on nonheme iron absorption of relatively small amounts of ascorbic acid either contained in or added to food during its preparation.[100,101,103,105] For example, 60 mg of ascorbic acid added to a meal of rice more than tripled absorption of iron[102] and 150 grams of papaya containing 66 mg of ascorbic acid increased iron absorption more than five fold when taken with a meal of maize.[105]

Animal tissues such as meat also greatly facilitate nonheme iron absorption. The substitution of 100 grams of beef for an equivalent amount of protein as egg albumin in a test meal increased absorption more than five times.[108] Meat is, therefore, doubly important: on the one hand as a source of heme iron and on the other because of its ability to enhance the absorption of nonheme iron. Inhibitors may be assumed to be present in large amounts in vegetal food because of the very low intrinsic availability of iron. Phosphates are known to impair iron absorption by the formation of insoluble complexes of iron within the duodenum. This is particularly true of phytate, illustrated by the pronounced inhibition of iron absorption by bran present in whole wheat bread.[109] Ethylenediamine tetraacetic acid (EDTA) is another blocking substance which, at levels employed as a food preservative in our diet, reduces iron absorption by effectively competing with the mucosal cell for iron.[108] As yet, studies of these dietary factors have not progressed sufficiently to define their relative importance in the American diet.

Perspectives

There can be no question of the widespread nature of iron deficiency. Anemia, which may have been an appropriate clinical measurement in past studies of nutritional anemia, is imprecise and often misleading as a screen for iron deficiency in the general population.[110,111] An extensive study by the World Health Organization indicated that iron deficient erythropoiesis, as identified by a transferrin saturation of less than 16 percent, occurs twice as frequently as iron deficiency anemia.[112] More recently, serum ferritin provides a means of evaluating tissue iron stores and defines a still larger group with iron depletion.[14,113] Such measurements leave no question but that a large portion, perhaps 20 percent of the world's 3.6 billion people, are iron depleted in the sense that adequate stores cannot be sustained despite near maximal absorption.

When women become overtly anemic due to iron lack, the cause is usually not an abnormality of mucosal cell function but rather ingestion of an insufficient quantity of available dietary iron or excessive losses of iron through bleeding or both. There has been a tendency to blame bleeding for most iron deficiency. Clearly bleeding in excess of 5 ml per day will exceed the limited capacity of dietary iron absorption. Clearly also, the most anemic persons in any population will be those who have bleeding superimposed on dietary limitations. While equating iron deficiency with blood loss is proper in men, this is not appropriate in vulnerable populations with increased iron requirements—for instance, infants, adolescents and menstruating and pregnant women. Current information indicates that the vast majority of the population with depleted iron stores appear to have only "physiologic" iron losses, adequately explained by an availability of about 5 percent of iron in meals not containing meat or significant amounts of ascorbic acid. The correlation between protein deficiency as measured by the serum albumin and iron deficiency lends support to the importance of meat in the diet.[113] Some compensation is achieved in some parts of the world by iron contamination of food resulting in an increased total iron intake of 150 to 200 percent that of native food.[114] Even so, dietary iron assimilation is borderline due to low availability. In developing countries availability appears to be

most critical whereas in developed countries the amount of iron ingested appears most limiting.

It is helpful to consider the adequacy of dietary iron in humans in relation to other species. All vertebrates have been faced with a hundredfold increase in iron requirements when heme became the vehicle for oxygen transport, yet iron deficiency is considered rare in most undomesticated species. Only in rats has iron balance been examined in detail and such studies show major differences from humans. The intake of dietary iron in rats is over 100 times that of humans when expressed per kilogram of body weight.[115] However, when these animals are placed on a restricted dietary iron supply, they can assimilate about 50 percent or more of nonheme iron of a type which would be of low availability (about 10 percent) in man.[116] Iron deficiency can be produced in rats only under the most stringent dietary restrictions and during periods of rapid growth.[117] Along with greater intake and more efficient absorption, these animals possess an effective system for excreting body iron through the gastrointestinal tract.[118] In man on his customary diet, the amount of iron which can be absorbed or excreted appears to be about 1 percent of that exchanged in rats, per kilogram of body weight.[115]

It seems reasonable to assume that man evolved his special ability to conserve iron, in response to a diet very low in iron and a low availability of dietary iron, through evolutionary changes which were valuable at the time they occurred. The similarity of iron exchange among Homo sapiens throughout the world indicates that this is a characteristic of man as a species and it must be presumed to have evolved long ago. The more difficult questions to answer are what constituted iron balance then and what changes have been imposed by civilization. Man's history as a highly skilled hunter with a strong dependence on animal food goes back at least a million years.[119] Meat is a portable concentrated food and in the paleolithic period it apparently was harvested from migrating herds and possibly stored by smoking or drying.[120] Fruit too, with its ascorbic acid content, may be presumed to have contributed significantly to dietary iron availability. In the comparatively recent history of man, profound changes in dietary habits seem to have occurred. The domestication of plants, occurring some 10,000 years ago, began the transition to predominately vegetable diets and the pressure of expanding human population made such low cost nutrients a necessity. It has been estimated that in less than 450 generations, the approximate contribution of animal foods in the diet has shrunk from about 70 to 5 percent.[119] Such changes would be anticipated to reduce the availability of dietary iron. Other more recent changes further reducing iron supply include a decreased physical activity and a parallel reduction in caloric and iron intake and the removal of contaminating iron from food. As a final insult, chelates have been added to prevent oxidation of preserved foods by metal ions and their presence acts to further reduce the availability of iron. Improved feeding has increased the size of infants, adolescents and adults with a parallel increase in iron requirement. It would seem that changes of civilization have confronted man with a dietary intake of iron inconsistent with his previously established genetic makeup. A similar line of reasoning may be applied to the iron deficiency observed in domesticated animals, such as pigs and wild animals held in captivity.

The solution to man's problem would appear simple; to provide additional iron to food and thereby realign dietary iron with man's needs. The acceptance of this philosophy is reflected in the fact that about 20 percent of iron intake in the United States and about 40 percent in Sweden is supplied by fortification of food. Such fortification has been carried out to date with no meaningful evaluation of its impact on iron balance. Indeed the effort may have been partially abortive since certain salts used for fortification have been shown to be of extremely low availability. Large particle ferrum reductum has been shown to be relatively unavailable;[121] sodium pyrophosphate is approximately 5 percent and ferric orthophosphate is about 30 percent available as reduced iron of small particle size or ferrous sulphate mixing completely with food iron.[122] Planning for fortification must then involve the use of available iron salts. To such planning must be added an appreciation of iron's availability in the diet eaten by a iron-depleted population. For example, Layrisse has shown that when as much as 60 mg of iron as ferric chloride is added to a meal not containing meat, this results in the absorption of only 0.3 mg of iron.[123] These considerations provide some initial guidelines to fortification. When the total iron content of the diet is low, supplemental iron of a high availability type may suffice; when iron content is more adequate but availability is very low, fortification of the diet with an enhancing substance such as ascorbic acid, rather than

adding additional iron, may be the more effective approach. While improving the iron nutrition of the population seems a worthy cause, its success will depend on further studies of food iron availability and on careful evaluation of the effectiveness of those dietary changes which are undertaken.

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Hypophosphatemia

These discussions are selected from the weekly staff conferences In the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Assistant Professor of Medicine, and H. David Watts, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, CA 94143.

DR. WILLIAMS:* *Today our Grand Rounds will be devoted to a finding often noted in our patients but rarely understood or evaluated fully: hypophosphatemia. Our discussant is Dr. Faith Fitzgerald, Assistant Professor of Medicine and Assistant Chief of Medical Service at San Francisco General Hospital.*

DR. FITZGERALD:† Thank you, Dr. Williams. The clinical problems associated with hypophosphatemia have only lately burst upon the medical ken. In the past, mention of phosphorus generally had to do with its increase in renal failure and its role as a pallid, usually well-behaved and predictable companion of calcium.

The attention now given to phosphorus in its own right has, in part, to do with its more frequent routine determination in automated systems and, most particularly, with the strong association of large numbers of hypophosphatemic states with iatrogenic maneuvers. As we have become more therapeutically vigorous, we have again created or magnified a disorder to the point where its deleterious effects become evident in numbers impossible to ignore.

Phosphorus depletion from dietary deficiency in nature is essentially unknown, as phosphorus is widely distributed in ordinary food. This makes teleological sense, insofar as phosphorus plays a major role in the structure of all mammalian cells and is a participant in the most fundamental reactions of aerobic and anaerobic metabolism.

In what clinical circumstances ought we to suspect potential hypophosphatemia? Hypophosphatemia, by which I mean serum phosphorus levels less than 3 mg per 100 ml, has been caused by: binding of phosphorus in the gut by nonabsorbable antacids; hemodialysis against phosphate-poor solutions (almost invariably in combination with antacid therapy); starvation and cachexia; acute and chronic alcoholism; hyperalimentation with phosphate-poor mixtures; intravenous administration of carbohydrates; hyperparathyroidism; rickets; osteomalacia; renal tubular defects; pregnancy; hypothyroidism; vitamin D excess and deficiency; alkalosis; acidosis,

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malabsorption; liver disease; hypokalemic and hypomagnesemic states, Gram-negative and Gram-positive sepsis; acute myocardial infarction; gout; administration of sex hormones, catecholamines and thiazides; diabetes, and genetic hypophosphatemia (Table 1).

Serum phosphorus levels usually remain between 3 and 4.5 mg per 100 ml with a diurnal variation and a postcibal mean fall of 0.25 mg per 100 ml below fasting levels in a normal person. This presumably occurs by the same mechanism by which intravenous carbohydrate loads induce a reduction in serum phosphate: phosphorus accompanies glucose entry into cells. It is evident that the serum phosphorus levels in a specimen drawn in the emergency room may be significantly higher than in one drawn several hours later on the ward if, in the meantime, intravenous administration of dextrose has been continuing. It may be by this mechanism that intravenous hyperalimentation induces such profound falls in serum phosphorus.

It is pertinent, particularly in the last regard, that the hypophosphatemia which normally accompanies the disposal of glucose is notably accentuated by fasting. Starvation, as in chronic alcoholics or candidates for hyperalimentation, may cause shunting of a carbohydrate load from liver to muscle. Perhaps, in the fasting state, less glucose enters the liver as glycogen and more is disposed of via glycolysis in peripheral tissues, using up serum phosphorus in the process.

TABLE 1.—*Hypophosphatemia: Causes and Associations*

Antacids: binding of phosphorus in the gut
Hemodialysis: against phosphate-poor bath
Starvation/Cachexia
Alcoholism
Hyperalimentation: with phosphate-poor solution
Carbohydrate administration: most pronounced intravenously
Hyperparathyroidism
Rickets/Osteomalacia
Renal tubular defects
Pregnancy
Hypothyroidism
Vitamin D deficiency or excess
Alkalosis
Acidosis
Malabsorption
Liver disease
Hypokalemia
Hypomagnesemia
Sepsis: Gram-negative and -positive
Acute myocardial infarction
Acute gout
Estrogens/Androgens
Catecholamine administration
Hyperventilation
Diabetic ketoacidosis
Genetic hypophosphatemia
Thiazide diuretics

Certainly we see our share of starved patients and of alcoholics with liver disease. How common is hypophosphatemia? In Britain, where these conditions are less frequently seen than at a county hospital in San Francisco, a 1972 study[1] showed that in 2 percent of all admitted patients, levels of serum phosphates were less than 2 mg per 100 ml. At the Oklahoma City Veterans Administration Hospital, it was found that in 42 percent of 106 patients admitted with the diagnosis of acute alcoholism, serum phosphorus levels were less than 3 mg per 100 ml, with values less than 2 mg per 100 ml in 10 percent.[2] I would anticipate that there might be similar findings in any hospital having a large number of malnourished alcoholic patients. It is not a statistically inconsequential problem.

What sort of clinical problem is it? What difference does it make? Several manifestations associated with hypophosphatemia have been described. I have taken the liberty of dividing these syndromes, scattered throughout the literature predominantly as case reports, into four major categories: neuromuscular, hematologic, hepatic and skeletal (Table 2).

Neuromuscular Manifestations

In Lotz's seminal paper in 1968[3] he described symptoms in patients rendered hypophosphatemic by phosphate binding magnesium-aluminum hydroxide antacids. The symptoms of his patients were like those noted earlier in experimental phosphate depletion studies in animals: weakness, malaise, anorexia, bone pain, joint stiffness and intention tremor. The severity of distress correlated with the level of serum phosphorus, with symptoms beginning at levels less than 2 mg per 100 ml. He suggested that the debility in some patients with hyperparathyroidism (bone and muscle pain, neurologic abnormalities and malaise) might be attributable to phosphate depletion rather than to the more commonly considered calcium abnormalities.

In another report[4] a young girl rendered hypophosphatemic by antacids and hemodialysis showed progressive severe muscle weakness involving the extremities, neck, and muscles of mastication, articulation and respiration. Anisocoria, ballismus and hyporeflexia were noted. Results of

electroencephalographic, electromyographic and nerve conduction studies were all abnormal, but returned to normal as serum phosphate rose.

Muscle contraction is known to be intimately dependent upon adenosine triphosphate (ATP) and organic phosphate compounds in muscle. Doctors Klock, Williams and Mentzer at San Francisco General Hospital recently published data[6] highly suggestive of a metabolic defect in muscle and liver in hypophosphatemia, with inhibition of glycogenolysis or glycolysis consequent to phosphate depletion. In their study, patients in whom serum phosphorus levels were below 0.5 mg per 100 ml were found to have abnormal responses to both ischemic exercise and to glucagon administration—suggesting interference with glycogenolysis in both liver and muscle. Both responses were returned to normal with correction of the hypophosphatemia.

TABLE 2.—*Hypophosphatemia: Syndromes and Abnormalities**

System and Syndrome	*Abnormality*
Neuromuscular	
Muscle weakness	Decreased CNS ATP
Anorexia	Inhibition of muscle
Intention tremor	Glycolytic pathways
Paresthesias	
Coma	
Convulsions	
Anisocoria	
Ballismus	
Hyporeflexia	
Ataxis	
Death	
Hematologic	
Erythrocytes	
Hemolytic anemia	Decreased ATP
Decreased oxygen release	Decreased 2,3-DPG
	? Abnormal membrane lipids
Leukocytes	
Decreased chemotaxis	Decreased ATP
Decreased phagocytosis	? Abnormal membrane lipids
Decreased killing	
Platelets	
Decreased clot retraction	Decreased ATP
Decreased survival *in vivo*	
Hepatic	
? Failure of compensatory 2,3-DPG—hepatic hypoxia	
Correlation with hepatic coma	
Skeletal	
Osteomalacia	Negative calcium balance with reabsorption
Arthritis	

*CNS = central nervous system, ATP = adenosine triphosphate, 2,3-DPG = 2,3-diphosphoglycerate.

A 50- to 80-percent decrease in brain cell ATP has been shown in hyperalimented hypophosphatemic dogs, with concurrent ataxia, convulsions and death.[6] Coma and convulsions in hypophosphatemic patients, again in the setting of hyperalimentation, have been reported.[7]

Hematologic Syndromes

Hematologic correlates of the hypophosphatemic state have been more extensively studied than any other. Abnormalities described include defects in red cells, leukocytes and platelets.

Erythrocytes

Two major categories of erythrocyte impairment have been studied in association with hypophosphatemia: those of structure and those of function. In mature red cells, ATP generation depends on the anaerobic metabolism of glucose (Figure 1). Adenosine triphophate synthesis occurs, mainly in the erythrocyte membrane, during the conversion of glyceraldehyde-3-phosphate to 3-phosphoglycerate. The source of phosphate for phosphorylation of glyceraldehyde-3-phosphate (and subsequently, adenosine diphosphate [ADP]) is the extracellular phosphate pool, from which inorganic phosphate enters into the membrane reaction predominantly by passive diffusion. Hence, changes in the concentration of intracellular phosphate can be produced by alterations of

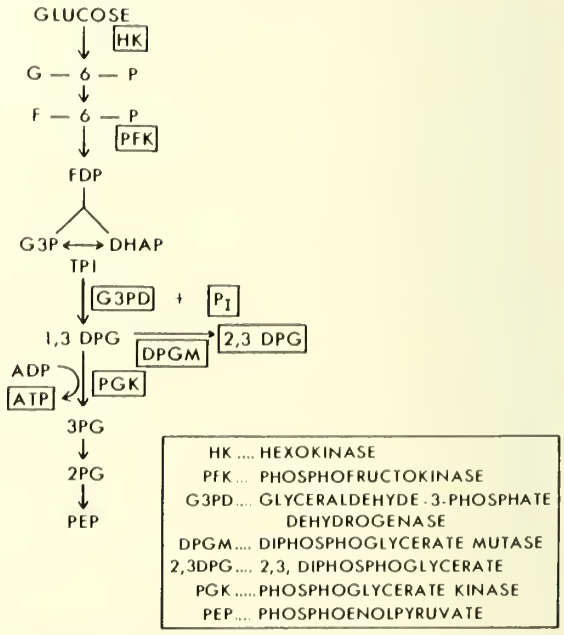

Figure 1.—The Embdon-Moyerhof pathway of erythrocyte glycolysis. Abbreviations are shown in the figure.

extracellular inorganic phosphate. An increase of serum phosphate, as in renal failure, stimulates glucose uptake and glycolysis at a number of points in the Embden-Meyerhof pathway; a decrease in extracellular phosphate has been clearly shown to have the converse effect, with a subsequent decrease in ATP production. The regulation appears most influential at the glyceraldehyde-3-phosphate dehydrogenase step, possibly because a considerable proportion of red blood cell glyceraldehyde-3-phosphate dehydrogenase is membrane bound and derives its substrate inorganic phosphorus directly from the extracellular inorganic phosphate pool.

Adenosine triphosphate is necessary for maintenance of erythrocyte membrane integrity and deformability and thus is very influential in determining red blood cell life span. *In vitro* studies show that ATP must be depressed to about 15 percent of normal levels before membrane rigidity and morphologic changes (spherocytosis) are detectable.[8] Actin and myosin-like microfilamentous proteins present in red blood cell membranes may be responsible for normal erythrocyte shape and plasticity. Insofar as actin and myosin in skeletal muscle requires ATP for controlled contraction, it is tempting to speculate that a similar phenomenon in hypophosphatemia may give rise to both red cell rigidity and to muscle weakness. Another possibility is that alterations in glycolysis affect the balance and stability of membrane lipids in red blood cells or that with severe ATP deficiency the sodium-potassium pump is itself compromised.

Whatever the mechanism, severe but reversible hemolytic anemia has been well documented in patients with profound hypophosphatemia (less than 0.2 mg per 100 ml, generally). Red blood cell ATP and 2,3-disphosphoglycerate were notably depressed (to 11 and 30 percent of normal, respectively). Striking reduction in erythrocyte ATP was associated with microspherocytic morphology, increased rigidity and diminished survival of the affected cells (^{51}Cr-survival time *in vivo* of one-fifth normal). All returned to normal after parenteral phosphate supplementation.[8]

Fortunately, despite pronounced reductions in serum phosphate, red blood cell ATP is rarely observed to fall much below 40 percent of normal, a condition tolerated remarkably well by the otherwise normal erythrocyte. The potential threat for red blood cell injury is compounded, however, by truly profound hypophosphatemia (during which red blood cell ATP may fall to less than 15 percent of normal) or by combinations (as in alcoholic or septic patients) of moderate ATP depletion and other disturbances of red blood cell integrity or of the microcirculation.

In addition to its role in the structural integrity of red blood cell membranes, serum phosphorus is intimately involved in basic erythrocyte function. The rate of red blood cell glycolysis and the passage of the intermediate 1,3-diphosphoglycerate through the glycolytic appendage (Rapoport-Luebering pathway) regulates intracrythrocytic 2,3-diphosphoglycerate concentration. Dr. George Sheldon of our own institution and others have done extensive work on the influences and consequences of hypophosphatemia on 2,3-diphosphoglycerate; specifically, on its integral association with the oxyhemoglobin dissociation curve and thus tissue oxygenation.[9]

Although the affinity for hemoglobin and the effect on oxygen binding of ATP and 2,3-diphosphoglycerate are similar, in red cells, the presence of three times as much 2,3-diphosphoglycerate as ATP makes the former quantitatively more important in this regard. The presence of 2,3-diphosphoglycerate and ATP decreases the affinity of hemoglobin for oxygen; the lower the 2,3-diphosphoglycerate, therefore, the greater the binding between oxygen and hemoglobin and the less readily released is oxygen to tissues (Figure 2).

In studies on patients hyperalimented without phosphate supplement, Dr. Sheldon found profound hypophosphatemia developing within ten days. Low serum phosphorus was associated with a

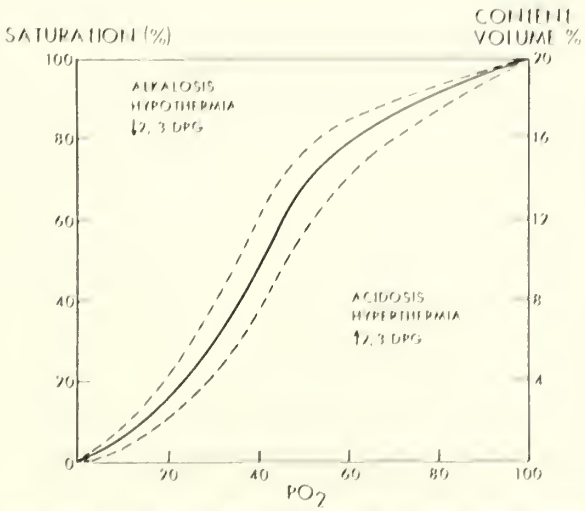

Figure 2.—Oxyhemoglobin dissociation and the effects thereon of acidosis, alkalosis, hypo- and hyperthermia, and 2,3-diphosphoglycerate (2,3-DPG).

measured decrease in red cell 2,3-diphosphoglycerate and ATP and with consequent increase in hemoglobin affinity for oxygen. This "shift to the left" of the oxyhemoglobin dissociation curve has been demonstrated in phosphate depletion in the absence of alkalosis and hypothermia (other factors increasing hemoglobin-oxygen binding) and in spite of factors which, in patients with normal serum phosphatic concentrations, "shift the curve to the right": fever, acidosis and liver disease.

With correction of serum phosphate concentration, red cell metabolism and oxygen release returned to normal. It is of interest that the fall in 2,3-diphosphoglycerate was generally more profound than that of ATP in hypophosphatemia; with phosphate repletion, 2,3-diphosphoglycerate regeneration took precedence over ATP repletion.[9]

Because of the known effects of 2,3-diphosphoglycerate depletion on tissue oxygenation, it has been proposed that the neuromuscular effects of hypophosphatemia are but those of tissue anoxia. However, Klock's data on muscle cell metabolic dysfunction in hypophosphatemia,[5] the demonstrated ATP depletion of central nervous system cells[6] and the observation that some patients with phosphate depletion are notably symptomatic at levels of tissue oxygenation well tolerated in chronically anemic patients suggest that the issue may be more complex.

Leukocytes

Another major hematologic abnormality of potential extensive consequence is the leukocytic dysfunction of hypophosphatemia. Severe hypophosphatemia induced by hyperalimentation in dogs resulted in a 50-percent depression of chemotactic, phagocytic and bactericidal activity of their granulocytes.[10] Concomitant reduction in white cell ATP was confirmed. The motility defect was corrected if cellular ATP was repleted by phosphate supplement of the animals *in vivo* or by *in vitro* incubation of the white cells in adenosine and phosphate. Functionally significant leukocyte ATP depletion has been shown at serum phosphate levels of 1 mg per 100 ml or less.

Phagocytes require ATP to form phagocytic vacuoles, the initial event in pathogen phagocytosis. The contractile apparatus in the granulocytic membrane responsible for amoeboid movement and pseudopod formation presumably requires ATP for actin activated myosin. Serum phosphorus may also play a role in the synthesis of organic phosphorus compounds required during phagocytosis, or for membrane synthesis.

It is well known that bacteremic and fungemic episodes are common in hyperalimented patients, a product of a prolonged indwelling line infusing delicious bacterial culture medium into a cachexic patient. Now add to this situation the potential for hypophosphatemic leukocyte dysfunction. In one study directed to this point, there was evidence of infection in 13 of 18 hypophosphatemic hyperalimented patients compared to but one of ten patients with normal phosphate levels.[10]

This phenomenon may play a role in the infection rate, notoriously high, in alcoholic, diabetic ketoacidotic and steroid cum antacid-treated patients—in all of whom there are other recognized states of white blood cell dysfunction in addition to the propensity to hypophosphatemia.

Platelets

The influence of hypophosphatemia on coagulation has received scant comment in the literature. Here, as elsewhere, phosphate depletion is villainous. Yawata and co-workers found that hypophosphatemic dogs hemorrhaged massively, with absent clot retraction and one-fourth normal ^{51}Cr platelet survival.[6] Platelet ATP depletion has been documented in hypophosphatemic states. Compound this with the thrombopathy of an alcoholic or a uremic patient, or note that many hypophosphatemic patients become so by overenthusiastic use of antacids given *because* they are bleeding. Realize also that if it is necessary to give a transfusion to a hypophosphatemic patient, the blood given may be bank blood, low in platelets and (if stored in low-phosphate anticoagulants) low in erythrocyte 2,3-diphosphoglycerate as well. We should, I think, pay more attention to serum phosphate levels in our bleeding patients.

Hepatic Syndromes

Of particular interest to us in this hospital are the data on the association between hepatic disease and hypophosphatemia. Most of those patients we see with liver disease here are chronic alcoholics, who have ample opportunity for hypophosphatemia. They are starved; some malabsorb from pancreatic disease. We give them intravenous glucose; they are often hypokalemic (which has been associated with a renal tubular phosphate leak) leading to an alkalotic state. Acute metabolic or (if they are hyperventilating from their withdrawal or liver disease) respiratory alkalosis

depresses plasma phosphorus, perhaps by shifting it into cells. Hyperphosphaturia and hypophosphatemia may follow the magnesium depletion which develops after prolonged ethanol ingestion.[2] Catecholamines, released in withdrawal, can lower serum phosphorus. Or if a patient is septic, phosphorus may fall. If a patient is acidotic from lactate or ketones, a compensatory phosphaturia may deplete him.

In an attempt to find out why patients with cirrhosis sometimes show hepatic decompensation under maximum therapy in the hospital, Rajan and co-workers studied serum phosphorus in liver disease.[11] He found that hypophosphatemic patients with cirrhosis tended to undergo greater hepatic decompensation than did patients with normal phosphate levels. He postulated that phosphate depletion, by inhibiting the normal compensatory increase found in erythrocyte 2,3-diphosphoglycerate in cirrhosis, contributed to greater hepatic hypoxemia. This—hepatic tissue hypoxemia caused by the "left shift" of the oxyhemoglobin dissociation curve in the presence of decreased 2,3-diphosphoglycerate—therefore could be responsible for progressive liver injury in malnourished alcoholic patients.

An association between the hypophosphatemic state and hepatic coma has been suggested. In one series, the postulate was that the hypophosphatemia was *caused by* the hepatic failure (both alcoholic and nonalcoholic). The speculation was that the hypophosphatemia represented phosphate shifts from extra- to intracellular space in buffering of the respiratory alkalosis of hepatic coma with resultant increased anaerobic glycolysis during hepatic coma with resultant increase in utilization of high energy phosphate bonds, thus consuming phosphorus.[12]

Skeletal Manifestations

Considering the role of phosphate in bone, it is not surprising that bony integrity may be compromised by phosphate depletion. A group at Kaiser Hospital in San Francisco recently reported four patients presenting with striking rheumatologic symptomy: large joint arthralgias, inflammatory arthritis and clinical-roentgenographic sacroiliitis so severe as to be initially misdiagnosed as ankylosing spondylitis. The patients all showed symptomatic improvement with correction of hypophosphatemia.[13]

Osteomalacia of severity sufficient to produce pathologic fractures has been noted in antacid-induced hypophosphatemia. The independence of this state from parathormone has been shown by its occurrence in several patients with surgically-caused hypoparathyroidism. Lotz and others have amply documented the physiologic response of the organism to hypophosphatemia.[14]

Physiologic Response to Hypophosphatemia

Rapid, profound decrease in urinary phosphorus

The decrease in urinary phosphorus in patients with hypophosphatemia is impressive. Essentially complete renal conservation occurs with losses which are extremely small relative to total body phosphorus. Clearance studies show that conservation exceeds that anticipated from decreased serum phosphate delivery to kidney alone. It has been suggested that there might exist an as yet undescribed "phosphorus-retaining" hormone, or that intratubular cell phosphate might be directly regulatory.

Hypercalciuria to values four to six times those in normal controls

In hypophosphatemia, hypercalciuria is of sufficient degree to produce a negative calcium balance. Some of the excreted calcium clearly comes from the reabsorption of bone, and no doubt contributes to the osteomalacia of hypophosphatemia. The hypercalciuria is reduced with phosphate repletion. Its dramatic presence has led to speculation that a chronically hypophosphatemic patient may have increased risk for nephrolithiasis.

Increased gastrointestinal absorption of calcium

Gastrointestinal absorption of calcium, in combination with bony reabsorption, is of sufficient magnitude to normalize serum calcium in surgically hypoparathyroid patients in the absence of vitamin D therapy. All of these effects are independent of parathyroid hormone.

These physiologic responses to hypophosphatemia become important in that they may lead to confusion with hyperparathyroidism: note that increased serum and urine calcium, decreased serum phosphorus, neuromuscular and bony complaints are common to both. If all occur in a patient with ulcer, the surgeon may be anxious to explore this classic case for parathyroid adenoma rather than simply decreasing the patient's antacid intake.

Similarly, a uremic patient's "metabolic bone disease" and "uremic neuropathy" may be relieved by tempering the vigor of antacid and hemodialytic therapy such that serum phosphate

is normalized. The use of antacids as prophylaxis for ulcer in patients on steroids may lead to phosphorus depletion, with bone disease or infection resultant from both steroids and hypophosphatemia.

Should we treat hypophosphatemia in the absence of symptoms? Certainly the data seem sufficiently impressive to suggest that we ought in all circumstances to prevent or correct those factors known to cause the hypophosphatemic state. Chances are, the serum phosphorus will then return to normal over the next several days without specific therapy.

In the face of manifest signs, symptoms or defects such as have been described, or with a serum phosphorus less than 1 mg per dl, my prejudice now is to treat. Regimes described in the literature include: for those patients able to take it by mouth, Phospho®-Soda (Fleet) 15 to 30 ml (80 to 160 mEq of phosphate) three times daily. If parenteral medication is required, monobasic potassium phosphate, 60 mEq administered intravenously three times a day, has been used with success.[5] The clinician must watch for a reciprocal lowering of serum calcium levels when phosphate is given (remembering that these patients are in negative calcium balance). Dairy food and other high calcium-phosphorus foods in the diet seem safest.

The teleological wisdom of nature was applauded when she guarded against dietary phosphate deficiency. Yet, given the fundamental role of ATP and organic phosphate compounds in living organisms, serum phosphorus seems most unteleologically vulnerable when one considers that it is presumably available in large quantities in bone. The great mystery, for such it remains, revolves around the question of where the phosphorus goes when it disappears from serum. The rapidity of change (hours to days) in the absence of urinary phosphate loss and, more telling yet, the return to normophosphatemia in the absence of supplementation in alcoholics, hyperalimented, antacid-treated, hemodialyzed and septic patients implies rapid fluxes between the intra- and extracellular spaces. Yet each investigator, working with his own set of cells, has presumed that the phosphorus so evidently missing from his system has gone into another. But in the absence of renal and gut phosphate loss (which are genuinely quantitatively insufficient to explain the majority of hypophosphatemic states) all tissues so far closely examined in hypophosphatemia have been phosphate deficient: erythrocytes, leukocytes, platelets, muscle, brain. We must await future study to answer these intriguing questions.

DR. WILLIAMS: *Thank you, Dr. Fitzgerald, for a very fine review. Dr. George Sheldon is with us today and, as noted by Dr. Fitzgerald, he has done a great deal of investigative work in this field. Dr. Sheldon, would you care to make any comments? We would be particularly interested in your thoughts on when and how to treat.*

DR. SHELDON:* I enjoyed very much hearing the excellent analysis of low phosphate problems. I have also enjoyed the interphase between the medical, surgical and pediatric services—each of which has looked at these problems from a different perspective. I think we are evolving some fundamental ideas about the significance of low phosphate syndromes.

One central question relates to whether low phosphate syndromes are purely an indirect effect of the well-documented change in red cells, and presume tissue hypoxia which comes from alterations in glycolytic intermediates such as ATP and 2,3-diphosphoglycerate. There is no question that as serum phosphate goes up and down, the glycolytic rate of red cells also increases or decreases in direct relation to serum inorganic phosphate levels. Unless phosphate levels are quite low (less than 1 mg per 100 ml) these changes do not become profound and one is reluctant to attribute all low phosphate symptoms to red cell deficiency. Although the red cell is a very specialized cell with no nucleus or mitochondria, it, in some way, is a biological biopsy specimen for other cells of the body. I think one may assume that if abnormalities are occurring in red cells secondary to low phosphate, some of these metabolic aberrations may be occurring in other cells of the body. This is a syndrome which relates to the importance of phosphate derivatives not only for energy metabolism but also for repletion of foodstuffs that occur throughout the entire organism.

One needs to separate catabolic versus anabolic low phosphate syndromes. Most instances reported which describe low phosphate syndromes are in patients who are nutritionally depleted for a variety of reasons. The low phosphate syndrome secondary to total parenteral nutrition is somewhat different from that associated with specific catabolic illnesses, such as uremia. A patient re-

*George F. Sheldon, MD, Chief of Trauma Service, San Francisco General Hospital, and Assistant Professor of Surgery, University of California, San Francisco.

ceiving total parenteral nourishment (TPN) is actively anabolizing dextrose and protein split products or amino acids, presumably to rebuild muscle mass, replace hepatic glycogen, and if excessive, may actually rebuild his fat sources. When anabolism is established, cellular requirements for potassium, phosphate, magnesium and other nutrients increase. We have found that an anabolic patient requires 20 mEq of potassium dihydrogen acid phosphate for every 1,000 nonprotein kilocalories. If this is administered to patients along with parenteral nutrition, serum inorganic phosphate levels will remain quite normal. If phosphate is given in excess of this, an incremental rise in serum inorganic phosphate levels will occur. If no phosphorus is given, a rapid drop in serum inorganic phosphate will occur, and if less than 20 mEq of potassium dihydrogen phosphate for every 1,000 kilocalories is administered, a slow but definite decline in serum inorganic phosphate levels will result.

The clinical application of this would seem to be relatively simple. Adequate phosphate to cover caloric intake needs to be provided. The scientific and biochemical aspects of this are more complex. Probably a minimal drop in serum inorganic phosphate is not harmful, and possibly elevation in inorganic phosphate may be helpful. We currently lack the answers to these questions.

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Important Advances in Clinical Medicine

Epitomes of Progress—Allergy

The Scientific Board of the California Medical Association presents the following inventory of items of progress in Allergy. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in Allergy which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Allergy of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, California Medical Association, 731 Market St., San Francisco, CA 94103

Occupational Causes of Asthma

EXPOSURE TO A NUMBER of irritating materials can produce paroxysms of asthma. In many instances, patients have a predisposition toward asthma. However, some materials seem capable of producing bronchial irritation and wheezing in patients who have had no previous respiratory difficulties.

Metal fumes, such as those from nickel and chromium, are well known for their ability to produce asthma and skin eruptions.

Toluene di-isocyanate (TDI) is an ingredient in the manufacture of polyurethanes. Polyurethanes are used in cushioning materials, insulation, varnishes and paint. Exposure to TDI can produce severe asthma. We have been particularly impressed with the frequency of asthma in automobile spray painters exposed to TDI.

Many patients, including some who are hairdressers, note exacerbation of asthmatic symptoms on exposure to hair spray preparations. A recent study has shown acute reversible narrowing of the small airways of healthy persons after exposure to hair spray. Studies were not done in asthmatic persons, but statements from patients would indicate that they may experience similar problems.

We have recently observed a number of meat wrappers with work-related respiratory symptoms. In addition to lacrimation and rhinorrhea, patients experience wheezing, coughing and dyspnea associated with cutting a polyvinyl chloride (PVC) meat wrap with a hot wire. Most, but not all, of the affected workers are cigarette smokers. A few are allergic and have had asthma in the past, but most have noted symptoms only after working with the hot wire cutting method. Antihistamines or bronchodilators (or a combination) and absence from work usually relieve the symptoms. The known chemical breakdown products of PVC include traces of such potent respiratory tract irritants as phosgene and hydrochloric acid. It is not known whether these materials are responsible for the difficulties.

This listing of occupational associations with asthma is by no means complete. It serves, however, to emphasize to physicians that a careful occupational history should be taken in all patients

with respiratory disease, particularly those who have asthma. In most instances, the precise mechanisms of diseases are unknown. Removal of the patient from his work environment is usually successful in eliminating the problem. Distressingly, a few patients continue to have moderate to severe asthma despite this change.

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Incidence of Certain Allergic Lung Diseases in California

ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS (ABA) and the hypersensitivity pneumonitides (HP) encompass syndromes manifested by lung damage and immunological changes. ABA, closely but not exclusively associated with asthma, is characterized clinically by recurring pulmonary infiltrates, proximal bronchiectasis, sputum and blood eosinophilia, and the expectoration of mucus plugs containing aspergillus elements. Immunologically, there are serum elevations of both immunoglobulin G (IgG) and immunoglobulin E (IgE), and a dual skin reaction to aspergillus extracts (immediate wheal and flare followed in 4 to 9 hours by a diffuse inflammatory reaction). Specific IgE antibodies as well as precipitating antibodies of the IgG and immunoglobulin M (IgM) classes to aspergillus antigens have been shown in these patients.

A large number of occupational and avocational diseases, such as farmer's lung and pigeon breeders' disease, are now classified as HP. In the acute form, fever chills, leukocytosis (but not necessarily eosinophilia) and pulmonary infiltrates occur some 4 to 8 hours after a heavy exposure to various organic dusts, usually of fungal or animal origin. In the more insidious type—perhaps the result of a smaller but more continuous exposure—early clinical manifestations include dyspnea on moderate exertion, productive cough and weight loss. Although an x-ray film of the chest may appear normal, pulmonary function tests will indicate restrictive lung disease with hypoxemia. Precipitins to antigens from organic dusts are found in the serum.

Only sporadic cases of these diseases have been reported from the Pacific Coast area. One of the limiting factors has been the availability of suitable antigens for precipitin tests. Using a battery of ten different antigens, over 260 sera have been investigated in patients either (1) suspected of ABA or HP or (2) with asthma and chronic lung diseases. About 25 percent had positive precipitins to one or more of the test antigens. The incidence of positive reactions rose to 75 percent and 49 percent when bird fanciers' disease and ABA, respectively, were suspected. Clinical correlation of these tests led to presumptive diagnosis of 12 new cases of allergic bronchopulmonary aspergillosis, five of bird fanciers' disease, and one of farmer's lung.

Thus, the results of this relatively small sampling suggest that these allergic lung conditions are not rare in California. Improved detection will require a combination of medical acumen and availability of standardized antigens and testing methods.

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Unreliability of Cytotoxic Food Testing

THE DIAGNOSIS of clinically significant food allergy is often difficult. The workup in suspected cases may include, after careful history taking, skin testing, and elimination and provocative diets—as indicated.

Additionally, the cytotoxic food test, an *in vitro* attempt to diagnose food allergy, has been used. The test consists of simultaneous incubation of blood cells (primarily polymorphonuclear leukocytes) with the appropriate antigen and the patient's serum. Positive reactions have been described by changes in the morphology of the leukocytes and red cells and the mobility of the leukocytes in the suspension.

In a recent control study of the cytotoxic food test, 45 patients were divided into three groups:

1. A control group of 20 persons with no history of symptomatic reactions to foods.

2. Fifteen atopic patients with well documented allergic reactions—consisting of urticaria, angioedema or anaphylaxis—to certain foods.

3. Ten persons who had less well defined reactions—such as headache, fatigue, dyspnea, maculopapular rash, nasal congestion or diarrhea—to certain foods.

When successive tests were run on the same patients, the results were not consistent. False positive reactions occurred with equal frequency in all patient groups, the food that provoked symptoms in atopic patients tested positive in only four of 15 with the cytotoxic test. Skin tests were carried out on 13 of the 15 atopic group two patients. In 11 patients, test reactions were positive for the foods provoking symptoms. The cytotoxic food test was not found to be a reliable method for diagnosing atopic reactions to foods. Also, claims that the test correlates with other untoward food reactions could not be corraborated.

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Misuse of Mist Therapy in Status Asthmaticus

MIST TENTS have often been used in the past for status asthmaticus with little rationale and even to the patients' detriment. Only a small portion of the mist inhaled reaches the lower respiratory tract, most of it being filtered out in the mouth and nasopharynx. Studies using aerosolized technetium from jet and ultrasonic nebulizers show that 70 to 96 percent of the particles are deposited in the upper airways, particularly during nasal inhalation. The usual amount of water that would be deposited in 24 hours in the lower airways of an adult is between 6 and 40 ml. The inspired air is normally fully saturated by the time it reaches the carina so that the benefit of a few milliliters of water in droplet form is remote. It serves basically to hydrate the anterior nares and upper airway. It is doubtful that inhaled mist provides a significant means of liquifying intraluminal mucous plugs.

On the other hand, mist therapy may be detrimental. The density of the fog in the mist tent is such that one cannot adequately visualize a patient in respiratory distress who needs close observation. It may also be very frightening to a young asthmatic patient.

In addition, aerosolized mist has been shown to increase airway resistance in asthmatic patients, particularly with the use of ultrasonically nebulized distilled water.

For this reason we do not recommend mist therapy in a patient with status asthmaticus. The only use for a tent in treating a patient with status asthmaticus is to supply humidified oxygen when the patient cannot tolerate a face mask or nasal delivery system.

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Hazards of Barbiturates in the Treatment of Asthma, Bronchitis, and Obstructive Pulmonary Disease

BARBITURATES ARE POTENT inducers of microsomal enzymes. In the liver, these enzymes hydrolyze both corticosteroids and theophylline, resulting in reduced biological activity for both substances. Furthermore, theophylline bioavailability has been shown to be adversely affected when theophylline is combined with phenobarbital in oral tablet form as compared with plain theophylline tablets. Thus, in a patient receiving oral tablets that contain both phenobarbital and theophylline, lower blood levels may be attained more slowly and the duration of these levels will be shorter. The same patient may well experience a lesser corticosteroid effect than the patient who receives theophylline without phenobarbital. These risks must be added to the established hazard of respiratory center depression, which occurs as a result of barbiturate administration.

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Newer Antiasthmatic Agents

THE OUTLOOK for the pharmacotherapy of asthma has been brightened in the past several years by advances in our understanding of the pharmacokinetics of theophylline. These have led to increased benefit from this medication in the introduction of alternate-day therapy with short-acting corticosteroids to minimize side effects of these drugs, and the addition of sodium cromolyn by inhalation, to our armamentarium.

The catecholamines act directly on the beta adrenergic receptor which activates adenyl cyclase resulting in increased synthesis of cyclic adenosine monophosphate (CAMP), while theophylline inhibits phosphodiesterase thus decreasing the degradation of intracellular CAMP. These agents act synergistically to increase CAMP levels. Drugs which increase intracellular CAMP cause bronchial relaxation as well as decrease release of mediators of immediate hypersensitivity, histamine and slow reacting substance of anaphylaxis (SRS-A).

New catecholamine bronchodilators have been introduced which stimulate the β-2 receptors in the lung to a greater degree than the β-1 receptors of the cardiovascular system. The three new compounds which have been studied most extensively are metaproterenol (Alupent® or Metapryn®), terbutaline and salbutamol. Metaproterenol is available in the United States in inhalable and oral forms and appears to be effective but not completely free of cardiovascular and agitation side effects. Terbutaline is currently available in the United States only in an injectable form (Bricanyl®) which offers little advantage to epinephrine except a slightly longer duration of action. Salbutamol (Albuterol®) is not yet available in this country but has been used widely in Europe and Latin America. Its advantages appear to be its long duration of action and potent β-2 effects with a minimum of side effects. Further clinical studies comparing these newer bronchodilators are under way to define their relative usefulness.

Another potential approach to pharmacotherapy in asthma is the use of α-adrenergic blockade. Few clinical data are available to date. In addition, the use of the cholinergic inhibitor atropine has also been reexplored since the increased emphasis on the importance of cholinergic stimuli in mediating bronchoconstriction. The prostaglandins E_1 and E_2 are potent bronchodilators and may be useful in the future. Finally, a sodium cromolyn derivative in an oral form (AH 7725) and beclomethasone, a steroid administered topically in low doses by inhalation without evidence of suppression of the hypothalamic-pituitary-adrenal axis, show therapeutic promise.

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Current Status of Bronchial Inhalation Challenge in Asthmatics

THE RATIONALE for the direct inhalation of suspected allergen extracts by extrinsic asthmatics is the possibility that immunoglobulin E (IgE) antibodies with specificity for the causative allergens may be present in the bronchial mucosa and better reflect the reactivity of the airway in asthma than skin fixed or serum IgE antibodies. The procedure employing inhalant allergen extracts is being used by many research laboratories in the hope that it will prove to be a more direct, accurate and relevant method to show the causative role of specific aeroallergens in asthma when there is a discrepancy between the clinical history and the skin tests. The inhalation test may also result in a more judicious selection of clinically relevant allergens in immunotherapy (hyposensitization), especially in asthmatic patients with multiple positive skin reactions and perennial asthma. It could also be used as a method to evaluate the effects of immunotherapy in asthma, as one study has shown that such therapy could result in changes in bronchial reactivity with or without concomitant clinical improvement of the disease.

Late reactions consisting of bronchospasm and a drop in pulmonary function about 4 to 6 hours following inhalation of allergens have been reported in some patients and make it imperative that such procedure be carried out with proper medical supervision, including provision for immediate admission to hospital.

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Asthmatics and Activity

ASTHMA IS BY FAR the commonest chronic condition noted in children's absence from school. Asthmatics are unique in that running for one to two minutes may elicit bronchodilation and increased performance, whereas if continued for five to twelve minutes bronchial spasm results, either during or within ten minutes following the exercise. This exercise-induced bronchospasm (EIB) can be prevented by premedication with sympathomimetics or cromolyn sodium.

Breathing exercises (diaphragmatic and chest muscle training) and physical fitness programs (cardiovascular and neuromuscular conditioning) have not been found to provide objective evidence of improved spirometric performance. Subjectively, however, patients often feel that such training has diminished their wheezing.

Certain guidelines emerge for consideration:

- Physical training and physical education within the peer group is endorsed for all but those with severe asthma.
- Use of a bronchodilator is recommended 10 to 15 minutes before activity for those developing significant wheezing on exertion. Occasionally a postexercise dose is also indicated.
- Intermittent short bursts of exertion for 1 to 2 minutes are preferable to steady, prolonged strenuous activity.
- Some competitive sports are possible for asthmatics. The patient and his physician should become acquainted with the rules governing medications for competitors. Athletic rules related to drugs should remain consistent with the needs of these athletes.
- Swimming seems to be the best sport for asthmatics. Golf, bowling, badminton, archery, softball or baseball, ping-pong and even soccer are generally safe, while football, basketball, handball, tennis and running are often too strenuous.
- Asthmatics have many remissions and exacerbations, and personal or supervisory monitoring is advisable. Respiratory infections, pollution, wind, dampness and cold weather tend to adversely interfere with health and performance. Retiring to the sidelines or, better yet, to alternate activity (library, cafeteria, classroom) should be respected.
- Continuing inservice training of school personnel (administrators, teachers, athletic instructors, nurses), appropriate alternative activities, suitable orientation of parents, and interposition of responsible and knowledgeable physicians as consultants are desirable.

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Adverse Reactions to Ampicillin

SINCE AMPICILLIN was introduced into medical practice in 1961, it has become the most widely prescribed antibiotic in the United States. Skin reactions have been reported to occur in from 7.3 to 9.5 percent of patient populations. Such reactions are unrelated to age but are slightly more frequent among females. It is important to know whether this high incidence represents an allergic reaction because of the potential danger from administration of this or related penicillin drugs.

The skin reactions are generally two types: a maculopapular one occurring in 68 percent and urticaria-angioedema in 32 percent of affected patients. The maculopapular eruption usually begins 7 to 10 days after initiation of ampicillin and persists 3 to 5 days whether or not treatment is continued. The typical distribution is originally truncal, spreading to the extremities, and most abundant at pressure areas. It may or may not be pruritic and pyrogenic. Two different collaborative groups have been unable to find an immunological basis for the maculopapular reaction. Hypothesized explanations for this skin reaction include the release of bacterial endotoxins, some other manifestation of the underlying disease or the presence of toxic impurities in the drug.

The less common urticarial reaction was shown to be immunologically mediated in about 25 percent of those studied. This finding was based on evidence from skin tests to ampicillin, penicillin G, penicilloyl polylysine (the major determinant) and other minor determinants as well as hemagglutination titres and readministration of the drug. Anaphylactic reactions to ampicillin are no more frequent than those from penicillin G.

A maculopapular eruption during or after ampicillin therapy is not an absolute contraindication either to readministration of ampicillin or

another penicillin. An urticarial reaction to ampicillin is more likely to be an allergic reaction. Further administration of any penicillin should be avoided unless penicillin sensitivity can be disproved.

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Rational Use of Oral Theophylline in the Treatment of Chronic Asthma

THEOPHYLLINE has been used effectively in the clinical management of chronic bronchial asthma for nearly 40 years. Until recently, however, the value of oral theophylline preparations has been controversial because of variable dose-response relationships and reports of severe and sometimes unpredictable toxicity.

Theophylline is thought to produce bronchodilatation by inhibiting the enzyme (phosphodiesterase) responsible for the conversion of cyclic adenosine monophosphate (CAMP) to 5′ adenosine monophosphate (AMP). This results in higher levels of CAMP which promotes smooth muscle relaxation and prevents release of chemical mediators from the mast cell and basophil.

Recent pharmacokinetic studies of theophylline have provided information necessary for a more rational approach in the dose scheduling of this drug. Theophylline is metabolized almost entirely in the liver (10 percent is excreted unchanged by the kidney). The rate of metabolism, however, varies considerably between subjects, resulting in a rather broad range of plasma half-lives. Plasma concentrations between 10 and 20 micrograms (μg) per ml appear to provide optimal therapeutic effect; but when the concentration exceeds 20 μg per ml, the chances of having adverse side effects are increased.

The narrow margin of safety between therapeutic and toxic blood levels, and the intersubject variability of plasma half lives demand individualized dosing schedules if optimal response is to be obtained without adverse effects.

For oral theophylline therapy we suggest using USP aminophylline tablets or one of several theophylline elixir equivalents. A reasonable starting dose would be 4 mg per kg of body weight per dose on a schedule of every six hours. Based on clinical response, adverse effects and plasma theophylline levels, the dose and schedule can be adjusted to achieve optimal clinical response with minimal adverse effects. When necessary a sympathomimetic drug, ephedrine or metaproterenol could be added in appropriate dosage if the patient's asthma is not controlled on theophylline alone.

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Recent Advances in Diagnosis and Treatment of Hymenoptera Hypersensitivity

ANAPHYLACTIC REACTIONS from stinging insects of the order Hymenoptera—particularly the honey bee, hornet, wasp, yellow jacket and fire ant—are a serious medical problem. The diagnosis of Hymenoptera hypersensitivity is based essentially on a clinical history, while skin testing is mainly confirmatory and used to determine the antigen dilution for the initiation of immunotherapy (hyposensitization). The preparations presently approved for both testing and treatment are commercially available whole body extracts (WBE) of insects. Reported clinical results of immunotherapy using these extracts are excellent as data from the American Academy of Allergy Insect Committee Registry have shown that over 95 percent of treated persons had either no reaction or much milder reaction when subsequently restung.

There is conflicting evidence in the literature regarding the correlation of skin test reactivity and the severity of the reactions to stings. There is also considerable overlap in the concentration of WBE which will induce positive skin tests in sensitive and nonsensitive persons. This warrants the search for more sensitive diagnostic tests and more relevant antigens for testing and treatment.

Recent *in vitro* studies using histamine release

from basophil leukocytes of hymenoptera sensitive patients using either WBE or pure venom have shown that while skin test reactivity to WBE correlated significantly with cell sensitivity in the most sensitive patients, the *in vitro* test using venom antigens could clearly distinguish sensitive persons from normals and suggests the superiority of venom antigens to WBE in this diagnostic system.

Two isolated case reports also suggest that venom antigens may be superior to WBE in the prophylactic immunotherapy of anaphylactic bee sting reactions.

Fractionation of bee venom in several laboratories strongly suggests that phospholipase A (PLA) is one of the major allergenic components which may not be present in detectable amounts in WBE.

A radioimmunoassay (RAST) appears a promising diagnostic *in vitro* test for the detection of immunoglobulin E (IgE) antibodies to venom and phospholipase A in the sera of hymenoptera sensitive patients.

While these findings are still experimental they may serve as a basis for a more specific approach to the improved diagnosis and treatment of Hymenoptera hypersensitivity. Isolated venoms are not currently available. In the meantime, whole body extract is recommended for therapy.

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Can Food Allergy Cause Asthma?

WHILE INHALANT ALLERGY (to pollens, house dust, molds, animal danders, and the like) is generally recognized as a frequent cause of asthma, food allergy of the delayed onset type is not. A substantial number of physicians, including some allergists, doubt the importance or even the existence of this type of food intolerance. However, there is steadily increasing acceptance of its importance, its frequency, its allergic nature and its association with asthma and the tension-fatigue (allergic toxemia) syndrome.

An important reason for failure to recognize delayed onset food allergy is the fact that in such allergy, results of skin tests are usually negative for the offending food or foods. Only in the immediate onset type of food allergy, in which symptoms appear soon after ingestion, are skin tests reliable. This type of food allergy, however, is usually well known to the patient before he comes to the physician, in which case such tests only confirm what is already known. In delayed onset food allergy symptoms do not appear for several hours after ingestion. This, plus the negative reactions to skin tests combine to make recognition of this type of food allergy difficult. Another characteristic is its tendency in some patients to be manifest chiefly in winter, while almost disappearing in summer. This adds further confusion.

A patient may like an offending food and not suspect it at all or believe he tolerates it well except on certain occasions, or in large amounts or in a certain form. An offending food is usually one which is eaten frequently such as milk (including cheese, yogurt, ice cream and sherbet), chocolate (including cola drinks) or corn (including corn sugar, dextrose, corn starch, popcorn and corn oil).

Delayed-onset food allergy and inhalant allergy often coexist. A frequent reason for a less than satisfactory result in treating inhalant allergy is nonrecognition of such a coexistence.

There are no laboratory tests—including the radioimmunoassay test (RAST)—or combination of tests presently available that are reliable in diagnosing delayed onset food allergy. Diagnosis is made by trial elimination diets. Diet directions should always be given to the patient in writing and should be adhered to for a test period of at least three weeks. The trial should be supervised preferably by a physician who has followed the diet himself for a minimum of 24 hours in order to be aware of the numerous errors that may occur.

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Allergy and School Children

APPROXIMATELY ONE in seven school age children has significant respiratory and other allergies. Children spend a large portion of their wakeful day at school. Their performance tends to parallel their health. School personnel often know little about the special needs of allergic students.

Allergic disorders are the commonest health problem noted in the school age population. It is desirable that school authorities, their local medical advisory boards, personal physicians and allergists develop more specific guidelines in behalf of children with allergies. Continuing inservice training is basic.

The following considerations are extremely important to the welfare of allergic school children:

- Physical education and sports. Children with allergies, particularly asthma, need understanding and appropriate encouragement.
- Respective functional roles for school nurses, classroom teachers, physical education instructors and administrators in identifying allergy reactions, dispensing medication, and notifying staff, parents and family physicians.
- Maintenance of allergy environmental control. Recognition and attention to the roles of dust, upholstery, dander, fur, feathers, carpets and pads, chalk, cosmetics, flowers, pollens, mildew, woodwork and metal dusts, printing, odors, chemical disinfectants, sprays, detergents, paints, hydrocarbons, construction and heating and ventilation systems.
- Respect for food allergies. Students have dietary restrictions due to their respiratory, gastrointestinal or skin allergies, and also to "allergic toxemia" (headaches, stomach aches, muscle aches, irritability, tiredness, pallor and the like). Understanding and cooperation are needed to allow these children to have their correct diets.
- Recognition of the vulnerability of allergic children to allergens (ingestants and inhalants), and the role of trigger factors (infections, smoking, emotions, pollutants, exertion, wind, humidity, inclement weather and the like) to cause substantial allergy distress.
- Awareness of the need of allergic children for their medications, and recognition of the frequent side effects from overmedication, particularly with antihistamines and bronchodilators.

It is incumbent upon those of us responsible for the health and welfare of children to properly attend to their special needs in school in a direct and purposeful way.

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EDITORIAL

The Changing Role of the Patient

MUCH HAS BEEN SAID and written in the past about the doctor-patient relationship and about the role of the patient in that time-honored and hallowed relationship. It need only be said that the role of the patient was usually a passive one. The doctor gave orders and the patient was expected to obey and seldom to ask any questions. The strength of this relationship was often very great. It was based on trust, confidence, wisdom, human understanding and some medical science. It was a very personal relationship. The doctor felt a personal responsibility for each of his patients and they turned to him for help, guidance and comfort in their times of illness, stress or trouble of any kind. This is the way it was.

With the growth of more medical science and more scientifically specialized patient care, the personal or human character of this relationship began to be eroded—by the doctor, not by the patient. Patients often became looked upon as examples of a disease, more or less interesting as the case might be. Mr. Jones or Mrs. Smith became "that coronary" or "that gallbladder." And there was much less interest in symptoms and complaints for which medical science could find no organic disease to cure or treat. In far too many instances the warm human person began to drop out of the doctor-patient relationship, and in this sense the role of the patient began to be depersonalized, or in the modern use of the term, perhaps even dehumanized. What had been a person had become a disease and the role of the patient had therefore changed.

This role of the patient as a kind of nonperson has been furthered by social, economic and polical events. Many of the social, economic and legislative programs which have come into being seem to view the patient more as a statistical entity which by law is entitled to health and health care, and for which health and health care must be assured to statistical satisfaction—rather than as a human being who is in personal trouble and needs help with his particular problem. There are good social, economic and legislative reasons for these events. But it cannot be denied that they have profoundly influenced the role of the patient and that their overall effect has been to depersonalize patient care even further by placing much of the decision making in other, more statistically oriented hands.

For a while it actually looked as though this depersonalization of the patient and the "statistification" of patient care might be the price that would have to be paid for scientific health care in today's world. But this was not to be so. Consummerism has appeared as a new force upon the scene and is making its presence felt in every aspect of health care. Consumers play a prominent role in much of the recent health care legislation, and the new legal doctrine of "informed consent" gives the patient himself a decisive role in determining what will or will not be done in his own case. This is clearly another and significant change in the role of the patient—and the consumer, whether he is a patient or not—in health care.

These new directions in the role of the patient and the health care consumer (however this is defined) are certainly not all bad. But neither are they all good. Perhaps most disturbing is the gradual weakening, if not displacement, of the doctor and the medical profession from decision making in health care. In the long run this cannot be good. True, it has been said that health and health care are too important to be left to the doctors. But on the other hand, the knowledge, expertise and even the opinions of the medical

profession are utterly essential if rational and workable decisions are to be made. These opinions should carry more than minimal weight in the decision making processes, wherever they occur in health care. Where this has not been done, the record shows the results tend to be very costly indeed.

The role of the patient in health care is certainly changing. The present directions, if carried to ultimate conclusion, will certainly prove unsatisfactory. The patient cannot be discounted as a person with personal problems. Nor can the patient or the public be expected to assume the professional role of the doctor or the medical profession. Yet both seem to be fundamental assumptions of present law. Further change is needed for the patient to achieve his or her role in his or her medical care. This will entail a better balance of the roles of doctor and patient inherent in the doctor-patient relationship, and a better understanding of the roles of both the medical profession and the society it serves in matters of health and health care.

This is a challenge for the leaders in both medicine and government—all of whom seem to be very busy doing a myriad of other things.

—MSMW

Improving Iron Nutrition

In this issue of The Western Journal of Medicine, the concluding sentence of an excellent review of iron metabolism and human iron requirement states, "While improving the iron nutrition of the population seems a worthy cause, its success will depend on further studies of food availability and on careful evaluation of the effectiveness of those dietary changes which are undertaken."

This tempered opinion does not describe what is actually happening.[1] On 15 October 1973 the Food and Drug Administration (FDA) mandated an increase (to 300 percent of present level) of the amount of iron to be added to all enriched bread and flour. This order was promulgated *without* further studies of food iron availability and *without* any evaluation of effectiveness or concern for the safety of people with iron-storage diseases. The basis for the FDA mandate has been carried in news releases from the Department of Health, Education, and Welfare stating that 95 percent of American women and children eat iron deficient diets. Iron deficiency is claimed to be the commonest form of malnutrition in the United States. These are grim statistics, if true, and the fortification of bread seems a sensible way to correct an easily correctable deficiency. This plausible argument for high-level fortification was presented by the Food and Nutrition Board of the National Academy of Sciences (FNB NAS) in November 1969. Six months later the FNB recommendation for high-level fortification was published as a formal proposal by the food industry (millers and bakers) in the *Federal Register* on 1 April 1970. The motion was promptly seconded by the Council on Foods and Nutrition of the American Medical Association. On 3 December 1971 the proposal was modified slightly by the FDA (the increase was scaled down from 400 to 300 percent), and it was finally mandated on 15 October 1973. On 13 February 1974 the new Commissioner put a stop action on this order, and public hearings were held in April. The findings of the judge were sent to the Commissioner in August. The Commissioner has not yet acted.

Why the five-year delay in implementing this plan to promote the general welfare? It is simply that the proponents of the plan have not investigated the safety and efficacy of their proposal, nor even recommended such investigation. Many physicians, especially hematologists, asked why the FDA permitted the shortcut. Permitted is too soft a word. The Agency has, in fact, assumed an advocacy position in the matter. Furthermore, instead of requiring of industry—and this is an industry program—evidence of safety and efficacy, the FDA has placed the burden of proof upon those who complain that the nutritionists and the millers and the bakers have not done their homework.

Meanwhile how does the nation suffer from the commonest cause of malnutrition, eating a diet that is inadequate in iron? Bluntly put, we suffer not at all. The American diet is "deficient" because the FNB NAS decrees that an adequate amount of iron for an American housewife must be 18 mg per day. Any woman who eats less eats a so-called iron deficient diet. But is such a woman iron deficient? The survey that showed an iron-deficient diet in 95 percent of women has also showed, on the basis of serum iron measurements, that only 1 percent of these women have iron deficiency.[2] What then is the basis of the 18-mg-per-day requirement? The basis is a considered opinion of a committee. The recommended daily allowances of the FNB NAS are inflated.

The matter of iron deficiency-equals-malnutrition has also been distorted. By definition iron deficiency exists when the iron stores of the body are filled not quite to capacity. This is malnutrition? If mild iron deficiency were a disease, then every blood donor would be sick.

Is mild iron deficiency anemia (IDA) a form of malnutrition? No one has showed any significant physical or psychologic deficit in women with mild-to-moderate IDA. Elwood, who has evaluated iron deficiency and its consequences in thousands of young women, found impairment only when the hemoglobin concentration is well below 10 grams per 100 ml.[3] The claim that mild iron deficiency is a form of malnutrition, a disease, is not quite justified. It serves a political purpose, but it is not justified.

Will supplemental iron in bread correct or prevent mild IDA? No one knows. Elwood's investigation involving hundreds of women in Wales showed that the effect on both correction and prevention of anemia was nil after nine months of fortified bread ad lib.[4] He has noted, "Although radioactive isotope studies suggest some iron preparations may be absorbed from bread under certain conditions, there is no proof the 'enriched' flour is an effective prophylactic measure against anemia."

Will supplemental iron in bread accelerate the course of disease in people with undiagnosed and preclinical hemochromatosis? Proponents of the program accept this as a probability, but they dismiss the plight of these people because there are so few of them.[5,6] How many people do have preclinical hemochromatosis? We do not know.

The FDA has a double responsibility reflected in its name: food and drugs. With regard to drugs the Agency is an adversary of industry. In the matter of food it has been a cousin. We physicians are keenly aware of the tight rein of the FDA when useful drugs are withheld for years while i's are dotted and t's are crossed in the massive documents required even for a new formulation of an old medicine. On the Food side of the house things are different. Industry can add flavorings, colorings, preservatives, fillers, vitamins, minerals—even iron—in whatever amounts so long as the additive is on a list of materials Generally Regarded As Safe, the GRAS list. No one has to prove them safe. The food industry regards them as safe. The mandated fortification of flour goes even beyond this. It is not a question of permitting iron in bread, but requiring it.

Why is the FDA a partisan in this matter instead of a judge? Agency rulings in nutritional matters have rarely been challenged. In this particular matter the proposal had been approved before the protests poured in. Industry proposals have been routinely rubber-stamped, especially when they come bearing the imprimatur of the National Academy of Sciences and the American Medical Association. But Industry is a presence even in these councils.[7] Even academicans among the membership are paid consultants, and their research is industry supported. Industry has friends also in the FDA. The stoutest proponent of iron-enrichment-now in the Division of Nutrition left the FDA last year to become an executive in the food industry, and his erstwhile boss more recently emerged from the bureau as an industry consultant here on the West Coast.

The moral of this tale? Perhaps that nutrition is too important to be left to nutritionists. The Bureau of Foods of the FDA should require scientific control of its mandates. That control has not been required by bureaucrats susceptible to the blandishments and pressures of the food industry. Recommendations for such control have not been forthcoming from committees dominated by the beneficiaries of Industry.

By this time the adversary positions on the mandate have been cast in ferroconcrete. The physicians insist that this substantial modification of the American diet should not be undertaken before safety and efficacy have been proved by pilot studies. The nutritionists, together with the bakers and millers, insist that good intentions backed by considered opinions must suffice. Up to now such benevolence has been all the FDA re-

quired. The new Commissioner, who inherited this headache, may insist that henceforth scientific considerations shall not be overridden by profits and politics.

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Severe Hypophosphatemia

A Previously Ignored Cause of Cellular Dysfunction

TWO RECENT, coincidental advances in hospital-based diagnostic and therapeutic techniques have focused attention on serum phosphorus levels. The development of the "twelve channel" apparatus in which several blood chemistries are obtained in semiautomated fashion has placed serum phosphorus in the routine category of blood chemistry determinations. The resulting increase in serum phosphorus data has quickly led to the perception that hypophosphatemia is not vanishingly rare, and in fact, may occur in more than 30 different clinical situations—as noted in the exhaustive review of the subject by Dr. Fitzgerald elsewhere in this issue. During this same period "intravenous hyperalimentation," the infusion of hypertonic solutions of amino acids and glucose, has become an increasingly popular therapy for the repletion of cachectic patients. In such patients extraordinary decrements in serum phosphorus (frequently below 0.5 mg per 100 ml) are commonplace in many surgical and pediatric units.

In our own institution, the University of Minnesota Hospitals, as many as eight patients receive such therapy at any time. From this experience we have described a potentially fatal syndrome which occurs in close association with the profound hypophosphatemia manifest by these patients.[1] Thus, shortly following development of hypophosphatemia, the patients suffer paresthesias, muscular weakness and lethargy, which may progress to convulsions and coma. At this time anemia regularly occurs, and its sudden onset and accompanying reticulocytosis suggest that its cause involves hemolysis. In many of the patients, mucosal bleeding develops, such as epistaxis and mild gastrointestinal hemorrhage; finally, severe infection—both bacterial and fungal—may occur in as many as two thirds of these patients.[2] As reviewed by Fitzgerald, evidence has been gathered that the anemia, hemostatic defects and infection propensity reflect adenosine triphosphate (ATP) deficiency in red cells, platelets and granulocytes, respectively—a deficiency caused, in turn, by the lessened availability of phosphate substrate for ATP synthesis by the blood cells.[3,4] Identical defects have been produced in starved, hyperalimented dogs in which, as in patients, complete reversibility of these abnormalities occurs when phosphate is supplemented.[5] The nature of the neurologic defects in hyperalimentation, although originally thought to reflect similar ATP deficiency in nerve cells, may be more complex. Certainly phosphate supplementation is not as dramatically efficacious in treating this part of the syndrome, and attempts to document brain ATP deficiency have to date not been successful.

It is possible that the neurologic symptoms and rapid muscular fatigability manifest in a hypophosphatemic patient may reflect a deficiency in another phosphorylated compound of red blood cells, 2,3 diphosphoglyceric acid (2,3 DPG). This organic phosphate compound, like ATP, is also critically dependent upon the availability of serum phosphate for its synthesis. Moreover, 2,3 DPG seems to be a crucial regulator of oxygen delivery to tissues; thus it binds to the hemoglobin molecule, thereby diminishing its affinity for oxygen.[6] Enhanced oxygen delivery to tissues results; conversely, oxygenation is predictably inefficient if red cells are deficient in 2,3 DPG. That cerebral hypoxia may occur during hypophosphatemia on this basis is suggested by observations in a profoundly hypophosphatemic, alcoholic patient who was infused with large quantities of sodium bicarbonate.[7] The patient rapidly became confused,

lapsed into coma and ceased spontaneous respirations, requiring mechanical support for the following 48 hours. Since alkalosis shifts the hemoglobin-oxygen saturation curve in the same direction as does 2,3 DPG deficiency (that is, to the "left"), the effects of bicarbonate and hypophosphatemia (and therefore 2,3 DPG deficiency) were additively, and crucially, deleterious to this patient.

Analogous considerations have suggested to Dr. Carroll Leevy that some confusional states noted in malnourished alcoholic patients may also reflect red cell 2,3 DPG deficiency with resulting cerebral hypoxia. Administration of phosphate to some such patients has improved their sensorium, while concomitantly increasing red cell 2,3 DPG and decreasing spinal fluid pyruvate and lactate levels (discussion in reference 1).

These observations indicate clearly that administration of alkali to hypophosphatemic persons may be particularly hazardous. Patients with diabetic, or uremic, acidosis are potential victims of such well-intentioned maneuvers. Thus, the acidotic diabetic patient upon entry to hospital frequently manifests diminished red cell 2,3 DPG levels. This deficiency results mainly from the inhibitory effect of acidosis on red cell glycolysis (and hence 2,3 DPG synthesis). The deficiency worsens if hypophosphatemia supervenes, as it often does, during insulin therapy. Fortunately, the predicted inefficient release of oxygen by hemoglobin in this situation is ameliorated by the opposing beneficial effect on oxygen unloading of acidosis itself (the Bohr effect). Rapid correction of acidosis by administration of alkali reverses this ameliorating effect which may partially account for the not-infrequent disasters encountered with bicarbonate therapy. Similarly, uremic patients are frequently treated with antacid chelators to reduce serum phosphate levels and thereby inhibit secondary hyperparathyroidism stimulated by hyperphosphatemia. Such therapy is frequently overly-vigorous so that patients actually become hypophosphatemic. Rapid correction of acidosis, especially by hemodialysis in these patients, may lead to tissue hypoxia—a sequence which probably, at least partially, explains the postdialysis syndrome of lethargy and weakness noted in many such patients.

It should be evident from the above and from Dr. Fitzgerald's excellent review, that serum phosphorus homeostasis is a critical area for future investigation. For the present, rigorous maintenance of serum phosphorus should prevent many of the previously-unperceived, deleterious consequences associated with its deficiency.

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Federal Support for Assumptions or for Science?

IN HIS PRESIDENTIAL ADDRESS to the Western Society for Clinical Investigation (which appears elsewhere in this issue), Dean Mason calls attention to a matter which should be of enormous concern to both the medical profession and the public. This is the substantial shift of dollar support away from basic research in medical science, which leads to new discoveries and fundamental progress, to programs which are expected to fill some presumed or assumed need for specific research to solve some specific unknown which will have significant impact in patient care. Further, substantial federal dollar support has been diverted entirely from support of medical research and is being used to impose costly yet untested assumptions on the health care delivery system. For example, there has been very little real testing of the assumptions inherent in Health Maintenance Organizations (HMO's), Professional Standards Review Organizations (PSRO's), the Health Services Agencies (HSA's) or of the approach of the Federal Drug Administration (FDA).

In retrospect this use of federal dollars to bring about an identified scientific or social purpose seems to stem from experience with the Manhattan Project during World War II. Here an enormous number of federal dollars was poured into a scientific project with a social (in this case military) purpose with an enormous and very tangible result. Now we seem to be trying for another Manhattan Project in health care delivery. The thing that appears to be forgotten is that without the basic scientific knowledge, a Manhattan Project type of approach will not succeed. The idea that if enough dollars are spent any assumption can be made to work is simply fallacious. Yet this is what we seem to be doing, and at the expense of federal support of the basic research which is the true well-spring of both scientific and social progress in health care and in the quality of life. As Mason says, this needs somehow to be brought to the public consciousness.

—MSMW

CORRECTION

In the case report "Cardiomegaly—A Possible Factor in Permanent Endocardial Pacing," which appeared in the April 1975 issue of THE WESTERN JOURNAL OF MEDICINE, the two photographs in Figure 2 (page 333) were exchanged inadvertently. They appear below as they should have been printed in the article.

Figure 2.—(Case 2) **Left,** Decompensated cardiomegaly with transient exit block. **Right,** Compensated cardiomegaly with capture.

CASE REPORTS

Refer to: Kuberski TT, Gabor EP, Boudreaux D: Disseminated strongyloidiasis—A complication of the immunosuppressed host. West J Med 122:504-508, Jun 1975

Disseminated Strongyloidiasis

A Complication of the Immunosuppressed Host

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INFECTION WITH Strongyloides stercoralis, a nematode intestinal parasite, usually is asymptomatic or produces only mild gastrointestinal symptoms in healthy persons. However, the infection can become fulminant and lethal when immunosuppression has been produced through natural or iatrogenic means.[1-12]

The present case of fatal strongyloidiasis developed in a young woman receiving chemotherapy for acute lymphoblastic leukemia. The patient had lived continuously in Los Angeles after immigrating from Costa Rica in 1956. The case is presented to emphasize the occult nature of Strongyloides infection in the United States and to point out the importance of diagnosing and treating this infection before beginning immunosuppressive therapy.

Report of a Case

A 31-year-old Costa Rican woman presented with complaints of fatigue, weakness and dizziness. Results of hematologic evaluation showed severe anemia, lymphocytosis and thrombocytopenia. A bone marrow aspirate was diagnostic of acute lymphoblastic leukemia.

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On admission to the University of California, Los Angeles, Medical Center on 16 March 1973, the patient said there had been no history of bleeding problems and had no gastrointestinal complaints. Except for obesity, findings on physical examination were unremarkable.

Laboratory data included: hemoglobin 10.7 grams; hematocrit 31.4 percent; leukocyte count 5,500 per cu mm with 61 percent undifferentiated cells. The platelet count was 66,000 per cu mm. Findings on kidney and liver function tests were within normal limits. Results of an intermediate-strength purified protein derivative of tuberculin and coccidioidin skin tests were negative; results of a skin test for mumps were positive. On a bone marrow aspirate, sheets of immature cells resembling lymphoblasts, very few normoblasts and myeloblasts and rare megakaryocytes were noted. Examination of three stool specimens showed no ova and parasites. One of 23 differential leukocyte counts showed a 13 percent eosinophilia with the remainder between 0 and 1 percent eosinophils.

Therapy with vincristine sulfate and prednisone resulted in a remission; after four weeks the peripheral blood count was normal and a bone marrow aspirate showed a hypocellular marrow with 5 to 10 percent degenerating blast cells. The patient was discharged on a maintenance regimen consisting of prednisone and 6-mercaptopurine, as well as isoniazid. The 6-mercaptopurine was eventually discontinued because of the development of leukopenia.

Two subsequent admissions to hospital were necessitated by high fever, chills, anemia, thrombocytopenia and the development of ulcerative perineal lesions. While the patient was in the hospital, no gastrointestinal or pulmonary abnormalities were observed. Numerous cultures of the blood, sputum, urine, stool, cerebrospinal fluid, throat and perineal lesions were negative for pathogenic organisms. No chemical abnormalities or pleocytosis were observed in the cerebrospinal fluid. The patient responded to corticosteroids, antibiotics and transfusion therapy with clinical defervescence and symptomatic improvement. The cutaneous perineal ulcers partially healed and on

discharge hemoglobin was 11.6 grams; hematocrit 33.6 percent; platelet count 120,000 and leukocyte count 6,000 per cu mm, with a differential of 46 percent segmented neutrophils, 3 percent bands, 46 percent lymphocytes and 3 percent eosinophils. Several bone marrow aspirates showed normal megakaryocytes, active erythropoiesis and granulopoiesis with no leukemic cells.

The patient remained well on no maintenance therapy until admission for the fourth time on 23 July 1973 following five days of nausea, vomiting and weakness, and an episode of hematemesis. According to the patient, there had been no abdominal pain, diarrhea, melena, fever or chills. On physical examination, the patient was seen to be obese, Cushingoid, alopecic, lethargic and pallid, with extensive purpura over the arms, chest and abdomen. Pulse was 140 beats per minute; blood pressure 98/70 mm of mercury; respirations 16 per min and temperature 37°C (98.6°F) orally. Diffuse, mild abdominal tenderness was noted on deep palpation with no rebound tenderness. Bowel sounds were hypoactive. A persistent extensive perianal rash with 3 cm area of ulceration was noted.

Initial laboratory studies showed a hemoglobin of 6.9 grams; hematocrit 19.5 percent; reticulocyte count 9 percent; leukocyte count 7,390 per cu mm, with a differential of 62 segmented neutrophils, 7 bands, 19 lymphocytes, 10 monocytes, 2 undifferentiated cells, 15 normoblasts and no eosinophils; platelet count 35,000 per cu mm. Results of a stool guaiac test were positive. Prothrombin activity was 88 percent; partial thromboplastin time 26.8 seconds; total protein 4.3 grams per 100 ml and albumin 1.9 grams per 100 ml. An x-ray film of the chest taken on admission showed old apical scarring and atelectasis in the right middle lobe. Dilated loops of small bowel with notably thickened edematous walls consistent with a paralytic ileus were seen on an x-ray of the abdomen (Figure 1). Blood, urine and sputum cultures were negative.

Supportive therapy was begun including nasogastric suction and blood transfusions. Three days after admission acute dyspnea developed with a respiratory rate of 40 to 60 per minute. The appearance of diffuse symmetrical alveolar infiltrates was noted on an x-ray film of the chest (Figure 2). Arterial partial pressure of oxygen (pO_2) was 28 mm of mercury, the partial pressure of carbon dioxide (pCO_2) 30 mm of mercury and the pH 7.49. Progressive respiratory distress with hemoptysis developed and intubation was re-

Figure 1.—Roentgenogram of the abdomen showing dilated loops of small bowel and the thickened, edematous intestinal wall.

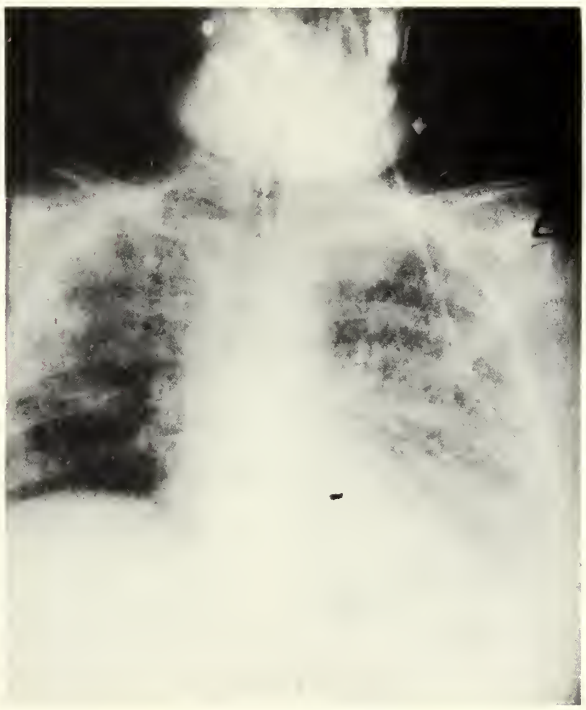

Figure 2.—Roentgenogram of the chest showing a diffuse symmetrical alveolar infiltrate.

quired. A tracheal aspirate failed to show Pneumocystis carinii, but filariform larvae of Strongyloides stercoralis were observed. Before specific therapy could be begun, a cardiorespiratory arrest occurred and the patient could not be resuscitated. Antemortem blood cultures were positive for Escherichia coli.

Postmortem Findings

Gross portmortem examination showed extensive bilateral pulmonary hemorrhage. The duodenum and proximal jejunum were distended and edematous. Most serosal and mucosal surfaces had petechiae and ecchymoses. The perineal and perianal skin was erythematous and abraded. There were several firm, irregular, marginated, maculopapular skin lesions several centimeters in diameter on the shoulders and thighs.

Microscopic examination of the skin lesions showed that the hypodermal adipose tissue contained many diffusely scattered filariform larvae of Strongyloides stercoralis. Sections of normal appearing skin failed to disclose larval forms. Histology of the lungs revealed alveolar hemorrhage with large numbers of larvae in the alveoli, septa, pleurae and blood vessels. Many larvae were present throughout the walls of the tracheobronchial tree, increasing in number toward the upper respiratory tract. Neither adult worms nor eggs were found in the respiratory tract. The heart, which grossly had small subendothelial hemorrhages, contained larvae in the chordae tendineae and within the endocardium of the atria and left ventricle. The jejunum, duodenum and ileum contained great numbers of rhabditiform and filariform larvae within all layers of their walls (Figure 3). Adult females and eggs, however, were generally confined to the mucosal and submucosal layers of the duodenum and jejunum. Diffuse colonic and prominent rectosigmoid mucosal petechiae were observed, with larval penetration of the colonic wall at various levels. An adult female was identified in only one extraintestinal location, the capsule of the pancreas. No adult males were identified. No parasites were seen in the spleen, reproductive organs or central nervous system. Many of the intrathoracic and mesenteric lymph nodes contained larvae. Larvae with bacteria in close association with the nematode cuticle were seen in various sites throughout the body. The wall of the inferior vena cava was thickened and hemorrhagic containing great numbers of larvae in a striking association with bacteria. Postmortem blood cultures were positive for Escherichia coli, Streptococcus faecalis and Enterobacter species.

Figure 3.—Histopathologic section of the jejunum illustrating the large number of parasites. Note a gravid adult female (F), eggs (e) and larvae (arrows) of Strongyloides stercoralis (Hematoxylin and eosin; reduced from × 140).

All lymphoid tissues showed pronounced lymphocyte depletion and in general, there was little or no inflammatory response to the parasites. The bone marrow was mildly hypoplastic with a relative predominance of the eosinophilic myeloid series. No bone marrow changes or infiltrates of body tissues consistent with leukemic relapse were found.

Discussion

The intestinal threadworm Strongyloides stercoralis is endemic in tropical and subtropical areas. In the United States this infection is usually seen in immigrants and travelers; however, small endemic foci do exist—primarily in some southern states and certain institutional settings.[4,13-15] The unique life cycle of this nematode explains the necessity of detecting asymptomatic infection in the immunosuppressed patient. Ordinarily Strongyloides infection in man has a low order of pathogenicity and is usually acquired by penetration of the skin by filariform larvae. The larvae enter the blood stream, migrate through the lungs, up the bronchi into the trachea and are swallowed to eventually reach the small intestine where they mature into adult forms. Eggs deposited in the submucosa of the small bowel hatch in the tissue into rhabditiform larvae which then enter the gut lumen and are passed in the stool. Infective filariform larvae develop in the soil from the rhabditiform larvae. In contrast to other nematodes, this

parasite is capable of autoinfection and can directly reinfect its host enabling it to persist for long periods.[1,14] It is not unusual for Strongyloides to be present within a host for many years, and it has been reported to persist for as long as 51 years.[6] Our patient lived continuously in nonendemic areas for 17 years; the case serves to emphasize the occult and persistent nature of this infection, even after the patient has left an area of endemicity.

The precise mechanisms involved in autoinfection are not well understood, but under ill-defined circumstances the rhabditiform stage undergoes transformation into infective filariform larvae within the gut before leaving the host. This allows reinfection of the host at a lower level of bowel or through the perianal skin contaminated by feces. The autoinfection phenomenon appears to be accelerated into a hyperinfective stage with depression of host immune defense mechanisms.[2-12,16] As in our case, the result was a rapid and overwhelming increase in the number of infective larvae and a fulminant, usually fatal form of strongyloidiasis. The recurring perineal ulcerative skin lesions seen in our patient were possibly due to skin maceration and scratching in response to the pruritis associated with larval penetration and continuing autoinfection. The significance of the skin lesions observed at postmortem on the thighs and shoulders of this patient was not appreciated clinically. Strongyloides stercoralis is a rare cause of cutaneous larva migrans, the skin lesions being mainly confined to the perianal and adjacent areas.[17] A search for serpiginous urticarial lesions over the thighs, buttocks and abdomen may assist clinicians in the early recognition of strongyloidiasis.

Strongyloides infection in the normal host can be asymptomatic and when symptoms are present, they are usually mild and may include epigastric pain, nausea, weight loss, diarrhea and vomiting.[13,18] Rarely, fatal or severe cases of strongyloidiasis can occur with exaggerated gastrointestinal symptoms, malabsorption, dehydration, paralytic ileus or peritonitis.[5,19-24] The severity of symptoms may possibly be related to the worm burden.[3] Since the symptoms of strongyloidiasis are relatively nonspecific, a high index of suspicion in addition to a suggestive geographical history, should be all that is necessary to consider this diagnosis. Detailed questioning of our patient produced no information that would have aroused suspicion of a chronic parasitic infection and three stool specimens failed to show any ova or parasites during the initial evaluation of the patient. Early dissemination may have occurred during initial chemotherapy at about the time of the brief eosinophilia. The use of corticosteroids in this patient may have suppressed the peripheral eosinophilia that is frequently seen in the immunologically intact host during worm migration, particularly where migration through the lung is occurring.[13] Lack of an eosinophil response in severe Strongyloides infection is thought to be associated with an impairment in the immune response and a poor prognosis.[12] The generalized lymphocyte depletion and lack of an inflammatory response to the parasite seen in our patient may reflect the depressed cell mediated immunity observed in other reported cases of fatal strongyloidiasis.[12]

The roentgenographic findings of dilated small intestine with notably thickened mucosal folds are consistent with strongyloidiasis[25] (Figure 1). These findings are presumably due to diffuse worm infection, lymphatic obstruction and allergic edema in the small bowel.[19,21] On roentgenograms of the chest, patchy bronchopneumonia can be seen when migration of the larvae through the lungs takes place. In heavy dissemination through the lungs, as seen in our patient, extensive pulmonary hemorrhage and bronchopneumonia can occur and are frequent causes of death.[1,4,6,7,10,13,20] The migrating larvae may produce tissue destruction and hemorrhage in the lung by their lytic action, as well as the mechanical and allergic irritation.[26]

Migrating larvae have also been implicated in the transport of bacteria from the gut into the circulation. This has been postulated as one of the mechanisms for the sepsis and meningitis due to enteric organisms which is not infrequently observed in fatal cases.[1,5,20,21,24] The response of the fever and clinical symptoms to conventional antibiotic therapy during the second and third admissions of our patient suggests this phenomenon may have been occurring with early parasite dissemination. The observed microscopic association of bacteria with larvae is consistent with this possibility and may explain the recurrent sepsis despite the presence of a normal leukocyte count and regenerating bone marrow. As is often the case, the Strongyloides infection in our patient only became apparent terminally when larvae were recovered from a tracheal aspirate. Parasites can occasionally be recovered from sputum,[5,10,27,28]

but this appears to be the first report of larvae being recovered by tracheal aspiration.

The diagnosis of Strongyloides infection is established by microscopic examination of feces or a duodenal aspirate and showing the strongylid larvae. The ova of Strongyloides are rarely detected in stools. Tests of stools can give negative results in more than 70 percent of cases despite careful examination of both routine and concentrated stool smears.[18] Negative findings on stool examination, such as obtained in our patient before chemotherapy was begun, is not unusual in persons in whom fatal strongyloidiasis develops later.[3,5] After immunosuppression it may be several weeks before larvae appear in stool.[5] A simple test-tube cultivation procedure may be a more efficient method of detection.[29] However, by duodenal aspiration the yield of recovery can approach 90 percent.[18] A recently described method using nylon yarn attached to a weighted gelatin capsule which is swallowed and allowed to pass into the duodenum may prove useful in the recovery of Strongyloides larvae from the small bowel.[30] The string is retrieved after several hours and the adherent bile stained mucus is examined for parasites. Therefore, if other methods have failed, examination of duodenal contents may be advisable before beginning immunosuppressive therapy in patients who are from known endemic areas. As with most infections due to helminths, the use of serologic and intradermal tests are not specific enough for use as diagnostic procedures.

Thiabendazole, in a dose of 25 mg per kg of body weight twice daily for two days, is highly effective in the treatment of Strongyloides infection in the nonimmunosuppressed host and has relatively few significant untoward effects.[31] The results using this drug in the immunosuppressed host, however, have been rather poor.[3,9,10,27,32] Thus disseminated strongyloidiasis is a potentially preventable opportunistic infection if the worm is erradicated before immunosuppressive therapy is begun. It might be reasonable, therefore, to administer a course of thiabendazole to patients who are highly suspect of harboring this parasite.

Summary

A hyperinfection syndrome due to Strongyloides stercoralis led to the death of a young woman during drug-induced remission from acute lymphoblastic leukemia. Before beginning chemotherapy there was no evidence of Strongyloides infection and the patient had not been in an area endemic for strongyloidiasis for 17 years. Larvae were recovered from a tracheal aspiration done during a catastrophic pulmonary event that led to the patient's death. On necropsy, fulminant and widespread dissemination of this nematode to virtually all organ systems was seen. The case is presented to emphasize the importance of considering this infection in the immunosuppressed host in the appropriate clinical setting.

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Small Versus Large Doses of Insulin in Diabetic Ketoacidosis

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THERE ARE STILL widespread differences of opinion regarding the amount of insulin which should be administered to patients in diabetic ketoacidosis. Many authors advocate administration of large amounts of insulin by both subcutaneous and intravenous routes in doses varying from 100 to 200 units as the initial dose.[1-10] Others have indicated that small doses are as effective as large doses.[11-17] Admission of the same patient with the same clinical situation to two different diabetes services gave an opportunity to compare two different dosage regimens.

Report of a Case

The patient is a 50-year-old white woman known as a labile diabetic who has been admitted 54 times for uncontrolled diabetes with varying degrees of ketoacidosis to several hospitals in the Los Angeles area within a three year period. More than 30 of these admissions were due to severe ketoacidosis and coma. It is interesting to note that most episodes of diabetes ketoacidosis were rapidly controlled, despite the fact that results of laboratory tests on admission usually indicated a pH of 7 or less and bicarbonate levels of 9 mEq per liter or less.

About five years before the period covered by this report, the patient had a total pancreatectomy as recommended by her physician at that time, in an effort to lower the high amounts of insulin she required. Since then, the daily dose has been 25 units of lente insulin with 5 units of semi-lente insulin; there has been no hyperglycemia between the ketoacidotic episodes.

Within a year, two admissions were to Service "A", and another three to Service "B". The admissions to either service were random and bore no correlation to the patient's condition at the time of admission. The biochemical changes and the different insulin dosage schedules are detailed in Table 1.

Results

Table 1 shows that within 12 hours of treatment, the total insulin dosage given on Service "A" was not more than 105 units—including the regular daily dose of isophane insulin suspension (NPH insulin)—and not more than 75 units of crystalline zinc insulin (CZI) during the first six hours. At Service "B", the patient received a total dose of 200 to 525 units of CZI (mean 325) at 12 hours, and a mean of 266 units within the first six hours.

Fluid replacement was similar in the two settings. Half normal saline totaling 2½ to 3 liters within the first six hours was administered on all admissions. Sodium bicarbonate ($NaHCO_3$) was given at Service "B" in two of the three episodes (one ampule only of $NaHCO_3$ of 44.6 mEq per 50 ml). On Service "B", the patient experienced severe to moderate hypoglycemic reactions during two of the three admissions, with glucose levels falling to as low as 37 mg per 100 ml. Intravenous dextrose administration was required.

Potassium (K+) levels which were in the range of 5.7 to 6.6 mEq per liter on admission were 4.1 to 4.9 at Service "A" after 12 hours. At Service "B" the K+ values were 3.5 to 4 at the end of 12 hours. At both services 15 to 30 mEq per liter of K+ (as potassium chloride) was given intravenously in the early stages of the treatment with the intravenous fluid replacement. All other results of laboratory tests (for sodium, chloride, hematocrit, blood urea nitrogen) and all vital signs (pulse rate, blood pressure, respiration rate, temperature) were within the same limits on admission to both services. No evidence of trauma, infection or other precipitating factors were found on admission. The rate of return toward normal of the bicarbonate was very similar during all admissions, as was the duration of large to moderate amounts of ketones in urine. The persistence of large amounts of ketones on the third

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Submitted, revised, November 4, 1974.

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admission to Service "B" may have been in part secondary to the hypoglycemia. The patient was initially confused to stuporous, and improved to full consciousness within 8 to 12 hours on all admissions.

Discussion

There are considerable differences of opinion among various authors concerning the amount of insulin recommended for the treatment of diabetic ketoacidosis.[1-16] Table 2 summarizes some of the recommendations for the insulin dosage for diabetic ketoacidosis. From the table it is obvious that while most authorities recommend initial doses of 50 to 200 units given intravenously, intramuscularly or subcutaneously in varying proportions, others recommend initial doses of 5 to 10 units given intramuscularly only. There are also differences of opinion concerning the criteria for subsequent insulin doses.

Smith and Martin[17] showed that patients given 80 units of insulin recover from ketoacidosis as rapidly as those given 240 units. Shaw and co-workers[11] showed that relatively small doses of insulin are effective in the treatment of diabetic ketoacidosis. According to these authors, there is a limit to the amount of insulin per unit of time which can effectively reestablish carbohydrate metabolism. Alberti and co-workers[13-15] showed recently that by treating patients in diabetic ketoacidosis with small doses of intramuscularly administered insulin (mean initial dose 16 units, followed by hourly doses of 5 to 10 units), the plasma-free fatty acids, glucose and blood glycerol fall substantially within the first hour. They found that low doses of insulin given intramuscularly were effective in the treatment of diabetic coma regardless of the severity of the metabolic disturbances. Their data showed no relationship between ketonemia or pH and insulin sensitivity.

In a report by Sönksen and associates,[12] patients given continuous intravenous insulin infusions of

TABLE 1.—*Chemical Characteristics of Five Admissions in Diabetic Ketoacidosis*

Hour	*Units of Insulin*	*Glucose mg per 100 ml*	*HCO_3 mEq/L*	*P_H*	*K^+ mEq/L*	*Urine S/A*
SERVICE A (Insulin: Small Doses)						
Admission 1						
0	CZI 50 SC	892	9	7.14	6.6	4+/L
4	CZI 25 SC	538	14	..	4.5	4+/L
8	Lente 25 & semi-lente 5	315	19	..	4.3	3+/L
12		205	19	..	4.1	3+/M
Admission 2						
0	CZI 50 SC	1,088	9	7.08	6.6	4+/L
4	CZI 25 SC	680	16	..	5.5	4+/L
8	Lente 25 & semi-lente 5	288	18	..	4.8	4+/L
12		175-250	22	..	4.9	3+/M
SERVICE B (Insulin: Large Doses—All CZI)						
Admission 1						
0	100 IV	890	3	7.06	5.7	4+/L
2	50 IV					
4	25 IV	345	8	..	3.6	4+/L
6	25 IV					
8	25 IV	131	9	..	3.5	4+/L
12		22	21	..	3.5	0/M
Admission 2						
0	100 IV	1,380	2	6.96	6.6	4+/L
2	200 IV					
4	100 IV	510	5	7.19	5.3	3+/L
8	100 IV	270	16	7.42	4.9	0/M
12	25 SC	83	22	7.41	4.0	0/M
Admission 3						
0	100 IV	768	5	7.08	6.4	4+/L
2	25 IV					
4	25 IV+25 SC	512	..	..	5.0	3+/L
8	25 SC	109	..	..	4.9	2+/L
12		27	19	..	3.6	0/L

SC = subcutaneous IV = intravenous S/A = sugar/acetone CZI = crystaline zinc insulin L = large M = moderate

5 to 10 units per hour achieved substantial plasma insulin levels. Alberti and co-workers[16] used a regimen of 5 to 10 units per hour of CZI continuously given intravenously in six patients with diabetic ketoacidosis, all of whom showed complete recovery.

In a recent case described by Shaw and associates[18] there was apparent failure of the low insulin regimen as recommended by Alberti and co-workers.[13] The failure occurred in a 76-year-old man whose diabetic ketoacidosis was apparently precipitated by a myocardial infarction. The patient was initially mildly hypotensive and in early congestive heart failure. Larger insulin doses were initiated simultaneously with adding intravenous administration to intramuscular administration.

As has been shown by Muller and co-workers[19] the highest serum levels of glucagon are found in patients with severe ketoacidosis. With insulin therapy, the glucagon levels return to normal. It is stated that hyperglucagonemia might be a factor in the ketoacidosis. However, the patient presented here had a total pancreatectomy and it is highly unlikely that high glucagon levels were present.

In the controversy of current interest concerning the efficacy of small doses of insulin in the therapy of diabetic ketoacidosis, our patient presents a comparison between two insulin regimens given to the same patient. Although it is impossible to create total equality of ketoacidotic episodes in the same patient on various occasions, reasonable similarity in the different episodes both clinically and chemically existed at the various

TABLE 2.—*Recommendations for Insulin Doses in the Treatment of Diabetic Ketoacidosis*

References	*Initial Dose*	*Subsequent Dose*
Bradley[1] (1971)	50-100u IV & 50-100u SC	after 1 hour: gl >300 mg per 100 ml— repeat initial dose; gl >600 mg per 100 ml— 150-200u IV and 150-200u IM; gl >1,000 mg per 100 ml—200-300u IV and 200-300u IM
Williams[2] (1974)	100 u IV or SC (or 1.5 u/kg)	50-100u (sometimes 200u) given hourly until gl <300 mg per 100 ml
Steinke[3] (1974)	serum acetone + at plasma dilution 50u if 1:4; 100u if 1:8; 200u if 1:16	reevaluation every 2-4 hours if gl >500 mg per 100 ml and serum acetone positive at 1:4 give 100u IV
Felig[4] (1974)	100u IV	50-100u every 2-4 hours until gl <250 mg per 100 ml or serum ketones show trace or negative
Jacobs[5] (1972)	100u IV & 200u SC	75-100u SC every hour until response is noted
Genuth[6] (1973)	50u IV and continuous infusion of IV 50u/hr	continuous IV 50u/hr until plasma acetone has decreased to trace or negative or gl <250 mg per 100 ml
Rabinowitz[7] (1972)	50-100u IV	after 1-2 hours, according to urine gl: 40u IV if 2% gl in urine and extra 10u IV for severe ketonuria until gl in urine is <1%
Hockaday[8] (1972)	serum ketones 3+ in plasma dilutions: 120u IV & 120u IM if 1:3; 80u IV & 180u SC if 1:1	after 1-2 hours: if blood gl has risen, double the initial dose. If blood gl unchanged, repeat initial dose. If gl falls 20%, repeat half initial dose
Shaw[11] (1962)	1.5u/kg (40% given IV & 60% given SC)	after 4 hours according to the formula: $\frac{\text{4th hr blood gl-200}}{\text{initial blood gl-4th hr blood gl}} \times \text{initial dose}$
Sönksen[12] (1972)	5-10u/hr IV in continuous infusion	continuous IV 5-10u/hr
Alberti[13-15] (1973)	10-20u IM	5-10u IM hourly

IV = intravenous SC = subcutaneous IM = intramuscularly gl = glucose.

admissions. On admission to Service "B", the results of laboratory tests showed a somewhat lower bicarbonate level in the patient on two occasions but the levels of pH, glucose and potassium were very similar on all admissions. Similar fluid and electrolyte replacements were administered. There were no differences in the vital signs and degree of consciousness. The rate of recovery of the patient was similar on all admissions. However, the potassium values were lower on Service "B" at the end of a 12-hour period and hypoglycemic reactions became a problem while on this (high insulin) service.

Insulin elimination from the body is accomplished by first-order kinetics.[16] The amount of insulin eliminated per unit of time is proportional to the amount of insulin in the body at that time. The half-life of intravenously given insulin as estimated by Rasio and co-workers[20] in serum and lymph is 7 to 13 minutes respectively. This half-life is the same for noninsulin-dependent diabetic persons as for nondiabetics,[21] while in insulin-treated diabetic persons, the insulin half-life is up to 40 minutes.[22] When insulin doses of 100 to 200 times the physiologic levels are given at frequent intervals, the increase in insulin levels is cumulative proportional to its half-life. Thus, if the half-life of a given subcutaneous dose is more than 30 minutes and additional amounts are given at hourly intervals, at the time of the second dose (one hour after the first), a substantial amount of the first dose will still be circulating and the subsequent levels will reflect this elevated "base line" plus the new dose. A stairstep phenomenon will result from each succeeding hourly dose. In other words, repeated frequent administration of large amounts of insulin may result in increasing amounts of insulin in the body, since each dose is given before total elimination of the previous dose.

The precipitating event in ketoacidosis is stress (infection, physical and emotional trauma, and the like) which causes rapid release of epinephrine and a more delayed release of growth hormone, testosterone and glucocorticoid hormones. Epinephrine causes elevation of blood glucose (glycogenolysis) and elevation of free fatty acids (lipolysis), the latter resulting in increased ketone body production. Growth hormone and glucocorticoid hormones contribute to the development of diabetic ketoacidosis through their actions on adipose tissue. As shown by Chernick and associates,[23] glucocorticoids—in the absence of insulin—limit the re-esterification of free fatty acids (FFA), ultimately leading to increased amounts of ketone bodies in the liver. In addition, glucocorticoids and growth hormone stimulate gluconeogenesis and ketogenesis respectively. Thus a diabetic patient in ketoacidosis is producing more glucose and more ketones than a diabetic patient under control because these enzyme pathways themselves are hypertrophied. As shown in the study of Sulway and co-workers,[24] elevated levels of acetone may persist for more than 24 hours despite adequate insulin administration. A finite amount of time is required for insulin to stimulate and reestablish "anabolic" pathways and suppress the hypertrophied "catabolic" metabolic pathways which have taken hours or days to develop. As shown by Sheldon and associates[25] and Kalkhoff and associates,[26] in the tissues of insulin-deficient animals, structural as well as enzymatic changes have taken place which may require 48 hours or more for correction and return to normal rate of action. Overtreatment and prolonged hypoglycemia can result if these physiologic principles are not taken into consideration. Large doses of insulin cannot speed the reversal of these metabolic events.

Summary

Considerable differences of opinion exist regarding the amount of insulin recommended for the treatment of diabetic ketoacidosis. Most authors advocate administration of large amounts of insulin, but others indicate that small doses are equally effective. Admissions of the same patient with the same clinical situation to two diabetes services gave an opportunity to compare small versus large insulin dosage regimens. On large doses of insulin, the patient experienced severe-to-moderate hypoglycemic reactions, and intravenous dextrose administration was required. On small doses of insulin, the recovery from severe biochemical and clinical ketoacidosis was as rapid as with the large doses but no hypoglycemia occurred. Large doses of insulin cannot accelerate reversal of metabolic events in diabetic ketoacidosis. Therefore, there seems to be no advantage in treating a ketoacidotic diabetic patient with large amounts of insulin.

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LETTERS *to the Editor*

More on Community Mental Health

To the Editor: Drs. Langsley and Barter, in their special article on Community Mental Health in California in the March issue [West J Med 122:271-276, Mar 1975], state that the major factor in the reduction of state hospital admission rates is the ability of the community programs to provide a full range of treatment.

There are many who would question this and attribute the lower rate to the Lanterman-Petris-Short Act which limits involuntary admission to state hospitals to those who are actively dangerous to themselves or others or so severely disabled as to not be able to care for themselves. Furthermore, voluntary admissions must be approved by the local mental health authority.

What isn't mentioned is the increased number of severely ill patients who are housed in board and care homes in communities that in many instances provide less in the way of treatment or rehabilitation than the state hospitals ever did. Communities have been "educated" to tolerate deviant behavior rather than correct or treat it.

It would be interesting to know the extent to which the percentage of patients (formerly able to receive treatment in state hospitals) receiving welfare and total disability compensation has increased and the extent to which psychopathology and disability have been reduced by the comprehensive forward-looking community program such as has been developed in Sacramento County. These questions are raised not in criticism of the worthwhile goal of treating patients in their communities, nor in defense of the many deficiencies that characterized previous approaches, but in the hope that truly valid criteria are developed for measuring and comparing the results of different treatment approaches. A change of locus in treatment is not in itself a valid criterion of success of a program. What have the changes been in mental health?

Norman Q. Brill, MD
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Vietnamese Refugee Children

To the Editor: The sudden influx of South Vietnamese orphans into our area has created the need for rapid dissemination of pertinent information to physicians who might be caring for these youngsters. Since I have not yet seen such information available, I would like to comment briefly on observations that I've made in seeing these children in South Vietnam in 1973 and now in my private practice of pediatrics. It is indeed important for any doctor caring for an orphan and his new family to spend extra time in considering the medical and psychological problems that the child may have, and in discussing the appropriate preventive and treatment factors with the parents.

The *"history"* that accompanies the child can be very misleading. Even the age of the orphan may be inaccurate, as the Vietnamese consider the child to be one year old at birth, increasing in age at each Tet New Year. Immunization records can usually be ignored; any vaccine given (if it indeed was actually given) might well have been outdated or attenuated by lack of proper storage. BCG tests are often given—so a positive TB skin test may be quite misguiding.

What we do know about the usual history of these children is more important to consider. The rampant malnutrition, manifested by anemia and lower serum albumin levels serves as a basis for many diseases not frequently seen in our private practices, but which must be considered upon the examination of any Indochinese orphan: tuberculosis, Pneumocystis carinii, are among those frequently encountered. Deaths from tuberculous peritonitis and Pneumocystis carinii are prevalent in Vietnam; cases of Pneumocystis carinii have already been reported among these children after arrival in the U.S.

We should all be aware that the parasitic infestations are widespread; however, we should keep in mind that typhoid and paratyphoid, amebiasis, hepatitis, measles, diphtheria, tetanus, dengue, and severe cases of chickenpox (not smallpox!) fill the hospital wards in Saigon.

I would like to recommend as baseline laboratory studies for all initial visits of these children:

CBC, stool cultures and studies for parasites, chest films, PPD skin tests, and urinalysis.

Time must be spent in counselling the parents about the care of these children. They are not used to our diet; many cannot tolerate milk very readily. They should slowly be exposed to American foods. It might be useful to introduce adoptive families to each other, so that they might meet with one another to exchange ideas and aids in communicating with and raising their newly-arrived children in this environment.

I hope that some of my ideas and observations will serve as some minimal guideline in caring for these children.

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That Word "Gurney"

TO THE EDITOR: Can anyone explain the origin of the word "gurney" which seems to be a purely Western United States term for "stretcher" (Eastern U.S.) or "trolley" (English)?

Webster defines it as "Western: a wheeled cot or stretcher. Probably from the name Gurney."

Who was Gurney?

DAVID V. THOMAS, MD
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* * *

TO THE EDITOR: In a conversation some years ago with the late Dr. Irwin Beede March, I mentioned having used the word gurney among army physicians at a post in the southern part of the United States and found that none of them knew it to mean wheeled stretcher. Dr. March said that he had had much the same experience in Eastern and Middle Western states and he speculated that gurney, in this meaning, was born in San Francisco. He told me that when he was a student at Cooper Medical College in San Francisco, beginning in 1906, a wheeled stretcher was a gurney.

In those years, he recalled, there was a horse-drawn carriage that supplied an off-hours transportation service to and from (among other places) the county hospital, and it was called the Gurney line. Medical students' hours of work and play were such that they used it often. The seats were benches running the length of the vehicle, as they do still on our cable cars.

Dr. March conjectured that some now-gone intern, departing for a frolicsome moment from the rigors of his duties and studies, pushed and perhaps half rode a wheeled stretcher through the corridors of the hospital, shouting, "Gurney line!"

This conjecture jibes pretty well with a letter from a Harry Magee of Oakland to newspaperman Dan Frishman, who used to write an entertaining and sometimes scholarly column for the San Francisco Examiner.[1] Mr. Magee, however, gives the route of the Gurney line as Berkeley to Oakland. Magee's letter to Frishman followed a few days after the Frishman column carried an item about the origin of gurney in the use here under discussion.[2]

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TO THE EDITOR: Over the years I have received many requests for an opinion on the source of the word "gurney" used to designate a wheeled stretcher, and have been offered an equal number of explanations, including that presented by Mr. Edwards, but none have proved satisfactory.

The problem with the view presented by Mr. Edwards that the word derives from a horse-drawn transportation service, available in San Francisco or, perhaps, Oakland is the inadequacy of the documentation. Now there was a Gurney Cab Company in San Francisco in 1891. Langley's Street Directory gives the address as 14 Montgomery Street. The company seems to have lasted for only one year. Neither before nor after 1891 can any evidence be found of its further presence. No such company appears to have existed in Oakland or the East Bay in so far as the sources available show. Further, unlike contemporary companies, there is no evidence that it ran a public coach service or that it was anything beyond a cab company. If the word "gurney" had local origin, there is of course the remote possibility that calling a stretcher after a bankrupt or "rattletrap" cab company, if well known, appealed to contemporary humor. But this is all speculation. If the vehicle was named after some local worthy who designed or made it, there were only two or three families of that name in the Bay Area of the times. None seem to have been associated with manufacturing or medicine. Although the name,

Gurney, is fairly common throughout the British Isles, surprisingly to this day the name is uncommon around the Bay (only two in the San Francisco phone book, five in Oakland—after three-quarters of a century).

Webster states that a "gurney" is not only a Western term for a "wheeled-cot," but is "probably from the name Gurney." This brings up a letter [to the editor, San Francisco Chronicle] of Mr. Clinton L. Jackson[1] of Oakland who quotes from Winton's loose-leaf encyclopedia that it was invented by Sir Goldsworthy Gurney [1793-1875]. Goldsworthy Gurney is well known as a Cornish physician turned inventor-chemist who gave lectures in London on electricity which the great Michael Faraday [1791-1867] found profitable. He is best known for his development of the steam carriage and steam-blast in locomotives to increase the furnace draft. He invented the lime-light used in lighthouses and for surveying and commonly known as the "Drummond Light" as first used by Thomas Drummond [1797-1840] in his survey of Ireland. He was knighted for his work in developing a system of heating and ventilation for the House of Commons. Although a good candidate as an eponymous source of the "gurney," I find no primary documentation that he was the inventor of the gurney, except for his secondary attribution.

The misleading factor in all this is the statement in Webster's dictionary that the term "gurney" is only used in the West—but without enquiring further or examining the possible philological origins of the word. On the contrary, the word "gurney" for a wheeled-stretcher is common in Scotland and Northern England and has been used in Scottish hospitals for many generations. It derives, I understand, from the word "gurn" (variously, girn, guern, gyrn), now obsolete in English, but still common in Scotland and Northern England, meaning "to show the teeth in pain; to snarl; to groan; to complain persistently; to be fretful or peevish." It is related to the word "grin" with metathesis of the "r," since one "grins in pain," but in Scottish dialetical use always carries the connotation of complaint and suffering. The same stem is seen in the word "gurnard" (a fish of the genus *Trigla* of the North Atlantic, in French, *grognard,* which, as anyone who has ever caught one knows, groans when it is pulled in). Any Scot, familiar with the "gurning" ("girning") of a peevish baby, instantly recognizes in "gurney" a vehicle for the suffering and those in pain.

The wheeled-litter came into general use during the Crimean War [1854-1856] at which time, as during the previous century, the overwhelming majority of military surgeons were Scots, such as John Hunter, Sir John Pringle, James Lind, Sir James McGrigor, George Guthrie. It has been said that some 80 percent of army and naval surgeons of the 18th and 19th centuries were from the Scottish schools of medicine. The term "gurney" would be instantly recognized by Scottish physicians as appropriate for such a conveyance. The various types of litters associated with the Crimean War were adopted during the American Civil War and will be found illustrated in the multi-volumed medical history of that war.

At the end of the last and the beginning of this century San Francisco had a large complement of Scottish trained surgeons in its hospitals from Pigne Dupuytren to George and Jack Shiels who would be familiar with the "gurney." It is inconceivable that the same piece of medical apparatus should have the same name in hospitals so far removed from one another as those of Scotland and the North of England and of California and the West without there being a connection. Consequently it seems to be that the word "gurney" is a Scottish term which has migrated West and is most appropriate as a name for a conveyance of those in pain.

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Refer to: Mason DT: The perennial challenge to modern clinical investigation (Informed Opinion). West J Med 122: 517-520, Jun 1975

Informed
OPINION

The Perennial Challenge to Modern Clinical Investigation

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AT THIS TIME during our annual meeting, it is expected that the president of this society should deliver a concise address of infinite wisdom taking into account all that is important in the pursuit of clinical investigation. Further, it is usually anticipated that—to be in tune with the contemporary interface between the academic world and society—the presidential address will focus on some issue of high significance relating public policy to clinical science. In considering the multiplicity of timely subjects which I might discuss, it struck me that the principal problems facing the performance of clinical investigation today are, perhaps in disguise, the same perplexities that have always been cause for concern to all of us who have devoted a major portion of our professional lives to medical research and education, and who wish to continue to do so in the future. What I have in mind is our concern for the proper balance between the three cardinal factors of ethics and resources and priorities on one hand, and scientific progress on the other. This I would term the perennial challenge to the clinical investigator. The important subject of ethics in clinical research has been well expounded upon by others; my remarks will be directed more to the problems of resources and priorities in medical science.

While no serious doubt exists, even at this time, that the development of new knowledge through biomedical research is essential for advancing the health of the American people, there is growing apprehension in the academic community regarding the size and direction of support allotted for the conduct of research. A genuine anxiety exists among many investigators that we may be living on borrowed time. Numerous questions have been raised concerning the development and delivery of medical knowledge: How should priorities be set for research programs? What should be the appropriate relation between investigation and health service needs? What is the proper balance between basic and clinical research? To what extent should investigation be targeted, as opposed to investigator-initiated? What should be the degree of support for the development of research manpower? And what role does research play in the education of the health professions? At an extreme, there is a segment of society which advocates that the whole of our medical resources and energies be centered on correcting the unfilled health delivery needs of the nation and there are those who, because of inflationary costs, demand fiscal ischemia solely for economy's sake by curtailing government spending in activities of least political significance. To say the least, the climate for the stable long-range support of medical science and

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education as we have known it in the past will clearly not be a part of the future. The ready availability of federal health dollars which flowered the monumental medical advances in the 20-year golden era of biomedical research following the Second World War has now been history for a full decade.

The complex and uncertain position of the support of medical science today is, of course, principally the result of a national desire for adaptations in our health system with public debate in recent years focused on revision of the balance between health care necessities and the development of new knowledge, the need for greater physician and related health care manpower, the reorganization of the health care delivery mechanism itself, and a means for assuring high quality health care provided at a controlled cost. These fluctuations in national health priorities have led to recent federal legislation establishing regional Professional Standards Review Organizations (PSROs), local Health Maintenance Organizations (HMOs) emphasizing prevention of illness, the Emergency Medical Service Systems Act and the major new Health Manpower Bill currently before Congress. The Health Manpower Bill would provide for nearly half of the total budgets of this nation's medical schools in exchange for substantial governmental involvement in enlargement of student enrollment, geographic distribution of graduates toward health scarcity areas and curtailment of certain specialty training programs in favor of increased primary care residencies. Also, a principal assumption underlying the Department of Health, Education and Welfare's Forward Plan for Health is that a form of national health insurance will be fully operative within the next five years. This augmentation of health care delivery programs contains some features which should substantially improve the health of our citizens, and I think that most of us in academic medicine would view certain of these measures as being salutary developments. Of grave concern to us, however, has been the unfortunate side effects of this recasting of the health industry of dangerously lowering the priorities and resources for biomedical research and neglecting the support of health research traineeships.

It does not require emphasizing to this audience that our health care system will become desperately crippled if biomedical research is allowed to wither, and a proper balance must be regained between patient care and investigation. Obviously, all of the health care that there is to deliver really represents the total evolution of medical knowledge resulting from critical analysis, both clinical and laboratory, through the ages. The number of clinical diseases that we can neither prevent nor cure is still enormous, and it is clear that no important inroads will be made without a return to a steady, purposeful expansion of basic and clinical research. Although there are claims to the contrary, in my opinion the gap is no longer between clinically useful knowledge and what is available to the public. Also, it should be pointed out to those who are obsessed with economics, research can play a vital role in improving the efficiency and diminishing the spiraling costs of the health care industry by developing improved therapy and preventive measures for presently unmanageable and incapacitating diseases. In addition, it is safe to say that medical teaching is best carried out in an atmosphere of scientific inquiry in order to translate the scholarly process of problem solving to patient care, so that the practice of medicine remains a learned profession rather than a skilled trade. The practical benefits of the education of physicians being based on a firm understanding of scientific principles are numerous. One example that comes immediately to my mind, relative to the discipline of cardiovascular medicine, is the recent clinical application of a new dimension in the treatment of refractory heart failure. This is the use of peripheral vasodilator agents for the relief of pulmonary congestion, elevation of cardiac output and reduction of myocardial ischemia. It became recognized as a rational, innovative therapeutic approach based entirely on an improved understanding of the physiologic factors regulating ventricular function.

How can we, the clinical academic community devoted to research into the course and treatment of human illness, make ourselves heard in a meaningful manner to effect a stable national policy regarding biomedical research? The Association of American Medical Colleges (AAMC) has emerged as a much needed and effective spokesman in Washington for medical research and education. Additional approaches are necessary, however, and they demand the best efforts of each of us. Probably our most important obligation is to improve our communication with the public who, after all, finance medical research. They have a right and need to know about our work, knowledge, problems and opportunities for progress as these relate to the betterment of society. We need

to make medicine less of a mystery and improve the art of talking about science with the press and news media.

I would like to conclude by bringing to your attention four recent undertakings in improving the state of scientific affairs in cardiovascular medicine. They were carried out by the professional subspecialty society with which I identify, and might well serve as useful endeavors for many of the other subspecialties within internal medicine—as well as the broad-based discipline of internal medicine itself. Concerning the first activity, the American College of Cardiology (ACC) recently completed a comprehensive National Institutes of Health (NIH) supported manpower study of cardiologists to define their current professional roles, to determine training objectives, to consider present and future manpower needs and to determine postgraduate educational requirements. Approximately 11,000 cardiologists were identified in active practice in the United States, resulting in a ratio of five such physicians per 100,000 population. Fifty percent are certified in internal medicine while only 10 percent have taken cardiovascular boards. Four general activity profiles of cardiologists were identified: noninstitutional internist-cardiologists, constituting a third of the total; noninstitutional clinical cardiologists, making up half of the manpower; institutional cardiac specialists, who largely constitute the remaining one sixth, and institutional academic cardiologists. On the basis of the high prevalence of cardiovascular disease, population growth and other factors, it was judged that approximately 5,000 additional cardiologists would be necessary by 1976 to obtain a needed six per 100,000 cardiologist-to-population ratio. In addition, this study defined the appropriate component needs of cardiology training programs and indicated the need for different types of programs to train different types of cardiologists.

Second, the ACC has established the Bethesda Conferences for exchange of ideas and formulation of policies by recognized authorities concerning matters of patient care, research and training in cardiovascular medicine. For example, the recent Conference on the Development and Introduction of New Cardiovascular Drugs brought together a large body of professionals in basic and clinical investigation, the pharmaceutical industry and regulatory government agencies to discuss problems concerning the timely and ethical development and clinical use of safe and effective drugs. A number of difficulties were identified, for which the participants jointly developed solutions. It was recommended that a Standing Advisory Committee be established composed of members of the ACC and the American Heart Association to consider criteria for efficacy and related issues in clinical cardiovascular pharmacology and therapeutics with the purpose of providing liaison between academic investigators, the Food and Drug Administration, the pharmaceutical industry and the National Heart and Lung Institute.

Third, the American College of Cardiology has initiated the development of a unique facility for postgraduate learning: construction of a national center for continued education, called Heart House, located in Bethesda adjacent to the NIH campus. The purpose of Heart House is to serve as the principal resource headquarters for the advanced teaching of cardiovascular medicine in which both group and self instruction are provided for, to afford a site for exploration of new teaching methods and to aid cardiovascular education throughout the nation and the world by development and distribution of all types of educational materials. In regard to postgraduate instruction, the American College of Cardiology also conducts approximately 35 regional scientific programs in cardiology each year in the United States through the coordination of the College's Committee on Continuing Education. In addition, the Self-Evaluation in Cardiology examination has recently been developed by the College in cooperation with the American Heart Association.

Fourth, the American College of Cardiology has organized the International Educational Program on Cardiovascular Diseases in cooperation with the Bureau of Education and Cultural Affairs of the United States State Department. This program provides the means for exchange of knowledge between the visiting faculty and host countries and affords the medical community of all nations opportunities in continuing education. During the past decade, the ACC faculty has carried out 40 such circuit courses and taught in approximately 50 countries around the world. This visiting educational program has established lasting friendships among physicians, governments and people of many nations—and has united across national borders those concerned with the treatment of heart disease.

In summary, my purpose has been to delineate

what I consider to be a perpetually consistent theme in the planning and performance of clinical investigation: the appropriate relation between—on one hand—proper ethics, availability of resources and health priorities and—on the other—the need for scientific advancements. This relationship may shift dramatically according to the overall necessities, economy and politics of our society. Our society and its representatives must come to grips with whether it is really wise to redistribute the federal budget towards military expenditures and over-involvement in foreign economies at the expense of pressing domestic needs, such as in health by withholding support of the growth and even maintenance of the medical sciences. In times past, resources for clinical investigation were relatively easily obtainable. However, today they are not and so the fruition of clinical investigation requires, among other attributes, considerable patience, much persistence and long hours of hard work, coupled with (perhaps the most important factor) an understanding spouse.

For optimal health care, it is axiomatic that medical research be reequilibrated with the health services. The waste of our most precious health resource is the loss of the research time of talented investigators with imaginative ideas that may ultimately lead to improvements in patient care, who are unable to carry out their work because of inadequate government planning for the support of the development of new knowledge. Perhaps I am somewhat of an optimist by nature, but I think that a growing body of congressional authorities are beginning to appreciate that augmentation of health research complements rather than competes with health care delivery. Nevertheless, we have a very long way to go.

Trauma Rounds

Chief Discussants
EUGENE S. KILGORE, JR, MD
WILLIAM L. NEWMEYER, III, MD

Editors
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This is one of a series of Conferences on Trauma at San Francisco General Hospital

Refer to: Kilgore ES Jr, Newmeyer WL III: Fingertip injuries (Trauma Rounds). West J Med 122:521-525, Jun 1975

Fingertip Injuries

LIONEL G. BROWN, MD:* Our first case (see Figure 1) is that of a 57-year-old healthy right-handed press brake operator. The patient had jacked his motor home up on blocks and it fell, crushing his right (major) index fingertip. There was no history of previous injury to the right arm or hand.

On examination, a volar-oblique amputation was seen of the soft tissue from the index finger, mid-middle phalanx, to the tip, exposing the insertion of the flexor profundus tendon and the bony phalanx. On the dorsum, the nail was avulsed. The patient was treated by a minimum of shortening of exposed bone under deep nerve block and tourniquet. A thin, split-thickness skin graft from the forearm was applied, he was given tetanus toxoid, and a course of penicillin. A short arm cast was applied. One week later, the cast was removed and there was a 90 percent graft takc.

Three weeks postinjury, there was a small open area on the radial side of the amputation stump which was regrafted. The injury then progressed to complete healing. Two months postinjury, the patient returned to work with minimal sensitivity of his stump and a useful finger. The patient does not desire that any further surgical procedures be done.

The second case is that of a 31-year-old healthy right-handed die setter who caught the tip of his major long finger between a crossbar and guard of a cup conveyor belt. This resulted in a subtotal amputation through the base of the distal phalanx. No previous injury or problem with the hand was noted.

On examination, total transection of the right long fingertip was noted, just distal to the interphalangeal joint, except for a paper thin, narrow hinge of midvolar skin.

Under deep nerve block anesthesia and tourniquet technique, the amputation was completed, saving a short flap of volar skin. A thin, split-thickness skin graft was applied, the ulnar three fingers were immobilized in a forearm cast, and the patient was started on a five-day course of prophylactic antibiotics. One week later the cast was removed and there was a 100 percent graft take.

DONALD D. TRUNKEY, MD:† *Twenty to 30 percent of all accidents involve the hand. Fingertip*

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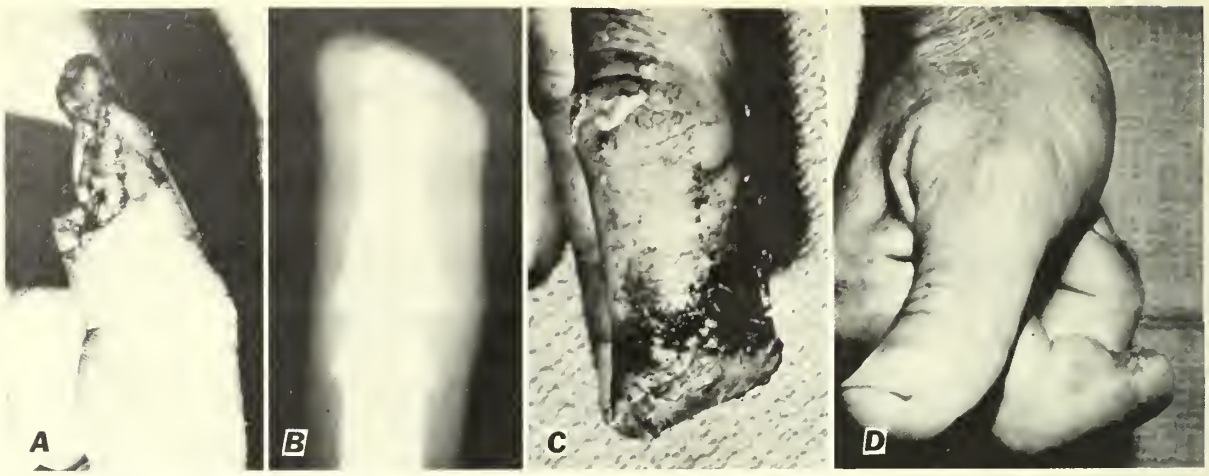

Figure 1.—A, injury in first case; **B**, x-ray film of index finger, first case; **C**, immediately following grafting; and **D**, three weeks after repair of injury.

injuries are so common that we have asked Dr. Eugene Kilgore and Dr. William Newmeyer to provide us with their concepts of proper management.

EUGENE S. KILGORE, JR, MD:* The disability caused by a fingertip injury is due to alteration in sensibility (that is, pain or numbness), loss of digital length, loss of stability of skin and bone, loss of endurance of skin to wear and tear, loss of nail function and nail cosmesis, and stiffness or deformity of the distal joint. This can be significantly reduced or enhanced by proper or improper treatment. One must appreciate that improper function of one digit tip may impair the function of the whole hand. Hence, the subject of fingertip injuries is important.

Injuries are either open or closed, tidy or untidy, dorsal or volar, radial or ulnar, or they involve the whole distal phalanx. Such categorization is important in considering treatment that will maintain basic function of the fingertip. The prime function of the distal phalanx rests on the following: (1) good sensibility without pain and adequate skin wearing quality on the surfaces that oppose in the act of pinch—for example, the ulnar side of the thumb and the radial sides of the index, long and ring fingers, (2) adequate length of the thumb and index (or the middle finger if the index is amputated), (3) stability of the skin, bone and distal joint and (4) adequate length of nails involved in picking up tiny objects.

Congestion develops rapidly after most injuries and is easily enhanced. All treatment must be directed toward its control, the elimination of dead space (for instance, clotted blood) and the restoration of good venous return and arterial flow. Throbbing pain is the prime signal of congestion and needs prompt physical rather than medical relief.

Most fingertip injuries are closed, being rendered by contusing or crushing forces. A congested fat pad or subungual hemorrhage that is very painful should be decompressed. To do this, we prefer to block the digital nerves and drill the nail or fat pad centrally with a No. 18 hypodermic needle mounted on a syringe. The hole remains patent for drainage if covered with a thick layer of zinc oxide ointment held in place with loose tube gauze.

Fractures are common and require serial x-ray studies for diagnosis and follow up. When there is little or no pain or significant displacement or instability, splinting may be optional, and at best, a padded metal guard on the digit. If pain is pronounced, a padded forearm boxing glove type of cast is recommended for a week or more to fully protect and rest the part. If there is significant displacement and instability, reduction and internal fixation is advised. For this, a longitudinally directed No. 19 hypodermic needle mounted on a 10 cc syringe is an excellent substitute if a Kirschner wire and drill is not available. The wire traverses the distal joint and is cut to allow protrusion well beyond the skin. It is usually withdrawn in four weeks, but the forearm cast may be replaced by a digit guard in one or two weeks. Administration of antibiotics is not necessary, but

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the finger should not be bathed until the pin is out. Basal intra-articular fractures may require an additional oblique small Kirschner wire, open reduction or even resection of the displaced fragment.

In the case of open injuries, the treatment will vary depending on how tidy or untidy the wound is. Prevention of infection can be achieved in most instances if dead space and circulation are satisfactorily attended to from the start, and if there is any doubt about either, antibiotics and antitetanus medications are immediately administered. Antibiotics are often applied to the wound during surgical procedures and given systemically at six hour intervals for at least two to three days. Tidy injuries are generally the result of puncture or cutting wounds. Puncture wounds are usually neglected. The patient keeps the digit active and dependent. In most instances he gets away with it, but occasionally seeks medical help because of progressive throbbing pain and the presence of a cellulitis or even an abscess (such as eponychia or paronychia on the dorsum, or felon on the volar aspect). The prophylactic treatment is elevation, immobilization and antibiotics. Treatment of an established abscess requires incision and drainage under tourniquet control and digital nerve block. The felon is drained where it points —usually in the center of the fat pad via a longitudinal incision. The nailfold abscess is drained by holding a No. 11 blade against the nail surface and scratching into the abscess which points into the crest of the nail fold. Drains are not needed if zinc oxide is kept on the wound for two to three days.

Tidy incisive injuries may be rendered without force by sharp metal or glass in which case the nail and bone are usually unharmed. When the cut is forceful, then the nail itself may be divided as well as the bone. Proper treatment requires the evacuation of clots under anesthesia and tourniquet control, as well as the use of 2 power loupe magnification. The wound may then be bathed with antibiotics and closed. We prefer 5-0 or 6-0 atraumatic monofilament nylon or Steristrips for skin closure. Fractures are treated as already mentioned under closed injuries.

Tidy amputations may be transverse or beveled and vary from split-thickness skin loss to loss of the whole distal phalanx. Over a period of 20 years, we have found that the most universally successful management has been the closure of any wound greater than 6 to 8 mm in diameter with a thin (for instance, 0.25 mm) split-thickness onlay skin graft taken from a volar-medial aspect of the forearm. This is delayed 24 to 48 hours if there is uncontrollable ooze or bleeding from the wound. This closure maintains length, reduces the chance of infection and makes it possible to start moving the digit and return to work quickly. Since most grafts shrink 50 percent or more, they tend to pull normal skin and fat over the defect to a sufficient degree in most instances to obviate any need for further time-consuming and costly surgical operations and disability. The graft is held in place with multiple strips of very narrow fine mesh Xeroform® gauze laid flat and smooth so as to stick and to close dead space. A stent of very wet gauze, tailored to the size of the graft, is placed on top of this and held with 6 cm strips of Reston® (1 cm and 2 cm wide) placed as sugar tongs over the digit at right angles to one another. This, in turn, is held with Tubegauze® or Kling®. A forearm cast is then applied to immobilize the wrist and injured digit. One or more adjacent normal fingers should be splinted along side the injured one for four to seven days to insure a 95 percent chance of a complete take (even on bone). A limited number of patients have symptomatic or troublesome stumps and need revision by shortening or the transfer of pedicle flaps. Full-thickness grafts (such as defatted fingertips) have not taken nearly as well as split-grafts and have not been functionally superior, so that we do not recommend them for fingertips. Reimplanted composite tips escharify and this only prolongs the disability. Amputation stumps in infants will generally epithelialize without grafting. When over half the distal phalanx of the thumb is tidily amputated, the filetted bone may be used with a tube pedicle to maintain its length. Sensibility can be restored with a neurovascular island pedicle. Tidy amputation of the whole distal phalanx may be considered for reimplantation with microsurgical techniques.

Untidy wounds about fingertips result from forces that cut and shred (for instance, cutting tools like saws and routers, and the like); forces that crush (hammers, heavy loads, closing doors); forces in motion that simultaneously crush and avulse (gears, conveyor belts, auto accidents, lariats, animal bites); and blasting and shattering forces (explosives, gun shots). The foremost problem is the hidden dimension of impaired circulation and the difficulty in determining viability of segments of tissue or of the whole distal phalanx. In some instances tissue survival may be

dependent on minimal amount of surgical dissection, suturing or other manipulation; while, in other cases, it may be dependent on the reduction and realignment of the displaced tissue. Whatever is done, however, must preclude any tissue tension. It is far better to leave a wound open and decongested than to close it and develop tension, dead space (and, possibly, infection) and set the stage for massive fibrosis.

In assessing viability, it may be better in certain cases to start debridement before inflation of the tourniquet, but once blood begins to obscure the tissue the arm (not finger) tourniquet must be inflated. A magnifying loupe should always be available.

Untidy lacerations of the volar fat pad may be closed with a few sutures if doing so does not cause tension, and there is infolding of skin margins or significant separation of the wounds without doing so. However, gently moulding the tissues and stabilizing them in position with strips of fine mesh Xeroform gauze, then strips of wet gauze, followed by Reston, in sugar tong fashion is often safer than sutures. Beware of trimming the ragged, though viable, edges of such wounds for fear of making the closure too tight.

Hopelessly mangled fingertips should generally be amputated and the stumps closed primarily or grafted. The loupe should be used to find and ligate the digital arteries with 6-0 nylon (not catgut, which is too reactive in the digit). The digital nerves should be similarly ligated and divided and allowed to retract into healthy fat. However, they must not be stretched.

A PHYSICIAN: *Would you describe the techniques used in the emergency room.*

WILLIAM L. NEWMEYER, III, MD:* I would like to respond to that question. Certain points of technique must be emphasized:

- The patient must be made comfortable (usually supine) during treatment.
- A tourniquet should be applied to the arm in every case and once tissue viability is established, inflated to 100 mm above systolic pressure. This is mandatory if pathology is to be properly assessed and dead space eliminated. Furthermore, in conjunction with anesthesia, it distracts the patient's attention from his anxiety and, contrary to belief, is well tolerated by young and old for 20 to 30 minutes. It is usually released after the wet dressing with gentle compression is applied.
- Two power loupe magnification and good light is essential.
- Skin preparation is with 1 percent or 2 percent solution of iodine in alcohol applied with a paint brush. This is kept out of the wound. The wound is moistened or irrigated with tap water.
- Anesthesia is rendered with 1 percent lidocaine without epinephrine. This is introduced through a ½ inch No. 26 calibre needle, slowly in small amounts (never enough to tense the tissues), in four quadrants at the base of the digit. A field block is given at the donor site for the skin graft.
- The instruments must be appropriate to do the job. For the most part, these should be plastic and include a sharp new razor blade and a clamp to hold it to take skin grafts. As mentioned, No. 19 or No. 18 hypodermic needles are good substitutes for Kirschner wires to stabilize fractures.
- Sutures should be nonreactive. We prefer monofilament nylon of 5-0 or 6-0 calibre (for instance, Prolene® with a "P" needle which is extremely sharp). Catgut, being reactive, is never used. The only exception is skin closure of infants where 6-0 plain catgut is used and obviates the agony of removing sutures.
- Dressings and immobilization make or break the case. They should protect the circulation and prevent dead space. Fine mesh Xeroform gauze applied in narrow strips, flush with the wound, keeps blood clots from forming about the surface and the suture knots. Beware of circumferential wrapping of gauze until a cushion of ¼ inch thick Reston is applied. Cast padding follows this and then, a fast-setting plaster cast as far as the mid-forearm to include the wrist. Wrist immobilization is essential for immobilization of the tip of a digit. One or more adjacent normal fingers should always be immobilized with the injured finger for the first few days. The thumb may be immobilized alone. Making a keel in the cast across the volar aspect of the wrist from mid palm to distal forearm gives the needed strength of the cast. The rest of the cast can be two or three layers thick for the sake of lightness, and cover the digits in a boxing glove fashion. All infants and other uncooperative patients need a long arm and heavier boxing glove cast of the whole hand for effective immobilization of even one digit tip. The

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hand is carefully cushioned with a roll of Kling or Kerlix® in the palm and Reston on the dorsum.

- Antibiotics should be directed at staph and strep and given prophylactically into all untidy wounds and continued systemically for at least two to three days at six-hour intervals. We are currently using lincomycin (500 mg every six hours) or cephalexin (250 mg every six hours).
- Elevation above the heart and release of all snug jewelry and clothing from the entire extremity is essential. This should be maintained for days, until the surgeon is satisfied that edema is not a problem.
- Analgesics are generally not needed. Significant pain requires inspection of the injury and if there is no tension then one is dealing with a psychological problem of a low pain threshold. Such patients generally do poorly regardless of treatment. If pain is throbbing, the tissue tension causing it must be released by physical means. This may require opening the skin or the wound.
- Dressings stuck to the wound should not be changed too frequently as long as the digit is comfortable. Simple lacerations and skin grafts may be changed in five to seven days. The dressings and splints of complex injuries to bone and nail bed are often best left alone for two to three weeks.
- The art of taking a skin graft requires a sterile towel on which lie a razor blade and a clamp to hold it, fine forceps without teeth, scissors to cut gauze, a strip of Xeroform gauze and four 2 × 2's. By "no touch" technique, these elements are kept sterile. The surgeon's hands are washed but ungloved. The donor site, the injured digit and adjacent digits are prepped with 1 percent or 2 percent iodine solution. Anesthesia is given. The extremity is elevated and the tourniquet inflated. A loupe is used to assure a thin even graft. The skin of the donor site on the volar inner aspect of the forearm is put under tension by one of the surgeon's hands wrapped behind the forearm and by a nurse tensing it behind the path of the razor blade. The blade is kept flat on the skin and advanced cautiously with rapid strokes by shoulder action and a stiff wrist. The graft is transferred to the digital wound by skidding off the blade. At times several grafts are needed. Sutures are unnecessary. They surgically traumatize the digit and provoke bleeding under the graft. The technique of dressing and splinting has already been described.

Refer to: Frankel RI: Clindamycin—Efficacy and toxicity (Medical Information). West J Med 122:526-530, Jun 1975

Clindamycin — Efficacy and Toxicity

RICHARD I. FRANKEL, MD, *Honolulu*

CLINDAMYCIN (CLEOCIN®), a member of the lincomycin group of antibiotics, is the 7-chloro-7-deoxy derivative of the parent compound lincomycin. The lincomycins are chemically unrelated to other antibiotics. Lincomycin, the first member of the group introduced for clinical use, has a spectrum and mechanism of action quite similar to that of erythromycin, and seemed to offer no clearcut advantage over the latter drug.[1] Clindamycin was found to have greater *in vitro* activity than lincomycin against some Gram-positive organisms, and to yield higher and more predictable serum levels than the parent compound;[2,3] it was therefore felt to be a more effective agent.

Although even early studies suggested no distinct advantage over other available agents in the treatment of Gram-positive infections,[4] nevertheless clindamycin has been suggested as a possible drug of choice in Group A beta-hemolytic streptococcal infection in all patients[5] or in patients allergic to penicillin,[6] and as an alternative when penicillins cannot be used in otitis media[7] and bacterial pneumonia.[8] Clindamycin has been suggested as a possible choice for the initial treatment of pneumonia thought to be secondary to Gram-positive bacteria or Mycoplasma pneumoniae infection,[9] although another study failed to show an effect of this agent on Mycoplasma pneumoniae pneumonia.[10] Indications listed in the 1974 *Physicians' Desk Reference* include upper and lower respiratory, skin and soft tissue streptococcal and staphylococcal infections, and upper and lower respiratory pneumococcal infections, as well as dental infections due to susceptible organisms.[11] It is presumably for the treatment of such conditions that physician prescription of clindamycin has increased dramatically, although increased usage of a variety of antibiotics seems to be a national trend.[12]

Clindamycin has gained such widespread physician acceptance that it is now one of the one hundred most often prescribed drugs in the United States. Data from The Queen's Medical Center in Honolulu (Table 1) illustrate the pronounced increase in the use of clindamycin since the introduction of the oral (1970) and parenteral (1973) preparations. Although clindamycin clearly may be effective in the therapy of a number of the infections referred to above, there are no data to show its superiority over other older agents of proven efficacy and safety, and lower cost.

Staphylococcus Aureus Infections

A clearer role for clindamycin has been shown in two types of infection. The first of these is in the therapy of infections caused by Staphylococcus aureus. Laboratory and clinical evidence of the efficacy of clindamycin against this organism has been published although the number of cases reported is not great.[13-15] Most strains of this species are inhibited by 0.1 microgram (μg) per ml of clindamycin; serum levels 50 to 100 times this are readily attained. For the first six months of 1974, susceptibility to clindamycin of all isolates of Staphylococcus aureus from our clinical laboratory by a standardized disc method[16] ranged from 94.6 to 100 percent.

The author has treated four patients with severe staphylococcal infection (two with endocarditis; one with facial cellulitis, bacteremia and pneumonia; one with bacteremia and multiple septic joints) with clindamycin because of intolerance to

TABLE 1.—*Yearly Volumes of Clindamycin Dispensed by the Pharmacy at The Queens Medical Center**

Year	*Oral (150mg tablets)*	*Parenteral (vials)*
1970†	3,840	..
1971	2,600	..
1972	4,200	..
1973	7,200	1,539
1974‡	21,400	6,326

*Data supplied by Ms. Nellie Chang, Director of Pharmacy, The Queen's Medical Center.

†Based on a five month period, adjusted to one year.

‡Based on a six month period, adjusted to one year.

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other antistaphylococcal agents. In one patient with endocarditis, the minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) for clindamycin were 0.1 μg per ml and 3.12 μg per ml respectively, and serum bactericidal activity was present at a 1:8 dilution 30 minutes after a 600 mg infusion. In the second endocarditis case, the MIC and MBC for clindamycin were 0.05 μg per ml and 1.56 μg per ml respectively. Serum bactericidal activity was not measured.

The first patient responded clinically to clindamycin, but bacteriologic cure could not be determined as the drug had to be discontinued because of the development of a rash. In the second patient, a rash developed shortly after starting the drug, and thus therapeutic effect could not be determined. The third patient completed a four-week course of clindamycin and was in good health when last seen approximately four months after discharge from the hospital. The fourth patient's blood was sterilized, but the patient died from underlying disease. Thus, clindamycin appears to be a reasonable alternative drug for severe staphylococcal infection in patients who cannot tolerate penicillins or cephalosporins or whose organism is resistant to these. Clindamycin or vancomycin could be used in such patients although it should be noted that neither of these agents passes readily into the cerebrospinal fluid.

Bacteroides Fragilis Infections

A large amount of literature has appeared in recent years indicating the importance of anaerobic bacteria as pathogenic agents in infections. However, misconceptions regarding such organisms appear to be common. When considering anaerobic pathogens, one must recognize that there are anaerobic Gram-positive cocci (for example, Peptococcus and Peptostreptococcus), anaerobic Gram-negative cocci (for example, Veillonella), anaerobic Gram-positive rods (for instance, Clostridium) and anaerobic nonspore-forming Gram-negative rods—the latter often referred to collectively, though incorrectly, as Bacteroides. Penicillin is very active against almost all strains of the first three groups, and is the drug of choice when one (or more) of these organisms is recovered from a clinical specimen.[17] A number of other agents, including clindamycin, can be used if the patient is allergic to penicillin or if there is simultaneous infection with a penicillin-resistant anaerobe.

There is still disagreement as to the proper classification of the nonspore-forming anaerobic Gram-negative rods,[18] and a new classification has been proposed.[19] These organisms belong to the family Bacteroidaceae, and the term Bacteroides should be reserved for only members of that genus. Speciation is important clinically for the following reasons. First, Bacteroides fragilis is the predominant member of the family in the gastrointestinal flora,[20] is part of the normal flora of the female genital tract[21] and is commonly found in infections originating in these sites, while other Bacteroidaceae predominate in infections originating in the oropharynx.[22] Second, while most Bacteroides fragilis strains are resistant to penicillin, most other species of Bacteroides (B. oralis, B. melaninogenicus) and almost all Fusobacterium species are susceptible to clinically attainable levels of penicillin.[23]

It is often difficult to evaluate the efficacy of antimicrobial therapy of anaerobic infections, as the infections are frequently polymicrobial—with aerobes as well as a variety of anaerobes being involved. Additionally, adjunctive therapy such as surgical drainage of an abscess or removal of necrotic tissue may be the most important therapeutic measure. Nevertheless, two studies[18,24] have shown that at least in certain groups of patients with Bacteroidaceae bacteremia, treatment with a drug to which the organism is susceptible *in vitro* results in a pronounced reduction in the mortality rate. There is now a large volume of laboratory[25-28] and clinical[18,24,29-33] data demonstrating the efficacy of clindamycin in the treatment of infections caused by the nonspore-forming anaerobic Gram-negative bacilli, and the author's clinical experience is in agreement with these data. On the other hand, no studies have shown that clindamycin is more effective clinically than other drugs to which the organism is susceptible *in vitro*. As already noted, anaerobic infections originating in the oropharynx are usually susceptible to penicillin, and in certain clinical settings Gram-positive anaerobes predictably susceptible to penicillin may predominate.[34] Additionally, certain species of Clostridium may be resistant to clindamycin.[35] Thus, one cannot select therapy for an anaerobic infection generally, but must consider which anaerobes are likely to be involved.

When considering the indications for use of a new drug, major considerations include three questions: (1) Is the new agent more effective than older agents? and (2) Is it less toxic than

older agents? and (3) Is it equivalent in efficacy and toxicity, but less expensive? As has been noted, there is no evidence that clindamycin is more efficacious than other agents to which the organism is susceptible. One must always be cautious of unrecognized toxicity of new drugs, and this will be discussed in more detail later. Regarding cost, clindamycin is considerably more expensive than penicillin, and also than most other agents which may be used in the treatment of anaerobic infections.[36] Therefore, usage of clindamycin in anaerobic infections should be limited to serious infections where Bacteroides fragilis is suspected or has been proven to be a pathogen. These will be mainly cases where the gastrointestinal tract or female genital tract are the probable portals of entry. Treatment may justifiably be started on suspicion of B. fragilis, as anaerobic cultures require more time for growth than do aerobic cultures, and even in the best of circumstances, some false-negative cultures can be expected. Once an organism has been isolated and susceptibility testing done by a standardized method,[37] then one can choose from the agents to which the organism is susceptible.

Clindamycin-Related Colitis

While gastrointestinal intolerance and particularly diarrhea were well-known side effects of lincomycin, a lower incidence of these adverse reactions with clindamycin was stressed as a feature of the newer derivative.[38,39] Many clinical studies of the efficacy of clindamycin emphasized the lack of toxicity, particularly with regard to the gastrointestinal tract.[2,4-7,13-15,29-31,38,40] Among the gastrointestinal side effects noted relatively early in clinical studies with lincomycin was a syndrome resembling acute ulcerative colitis with fever, leukocytosis, abdominal pain and severe diarrhea, sometimes with blood and mucus in the stool.[41,42] In spite of case reports attributing this pseudomembranous colitis to lincomycin,[43,44] little attention was given to this syndrome over the next few years, presumably because gastrointestinal complications, including occasional cases of an identical syndrome, are recognized as complications of a variety of antibiotics.[45,46]

The occurrence of this syndrome following the administration of clindamycin was not reported until Cohen and co-workers[47] described three cases and alluded to another three they had seen. A subsequent article describing seven cases of pseudomembranous colitis associated with lincomycin[48] was followed by a number of letters to the editor[49-57] and case reports[58-64] which have shed light on the epidemiology of, and illustrated the clinical features of, the clindamycin-associated illness. Of the patients described in references 47 and 49 through 64 (patients in reference 62 are not included, as they are also described in reference 63), 25 are described in sufficient detail to extract the clinical information presented in Table 2.

The clinical features include relatively sudden onset of fever, abdominal pain and sometimes distention, and severe diarrhea—often with blood or mucus or both in the stool—occurring most often during but not infrequently after a course of clindamycin. This is most often seen with orally administered clindamycin, but may occur with intravenous administration of the drug as well. Although the manufacturer has felt that the occurrence of colitis is unrelated to the occurrence of simple diarrhea during treatment,[51] such diarrhea during treatment did occur in two of three patients in whom colitis developed after the course of clindamycin had been completed. In the other three patients with similarly timed onset of colitis, no mention is made of the presence or absence of diarrhea during therapy, though in one patient diarrhea and cramps had previously developed in relation to a course of lincomycin.[64]

TABLE 2.—*Clinical Features of 25 Cases of Clindamycin-Related Colitis*

	Number of Patients
Temporal relation of onset of colitis to clindamycin therapy	
During treatment	19
After treatment	6
Route of administration of clindamycin	
Oral	21
Intravenous	3
Not stated	1
Course of colitis	
Single episode	23
Recurrent disease	2
Corticosteroid therapy	
Not required, or required for less than one month	22
Required for longer than one month	3
Colectomy	
Not required	24
Required	1
Death directly related to colitis	
Did not occur	21
Occurred	4

The possibility that the colitis may be aggravated by opiates or their derivatives[51] is supported by several of the cases reported in the literature. Particularly grave features of the illness include the possibility of recurrent colitis,[54,64] the necessity for prolonged corticosteroid treatment,[47,50,54] the necessity for colectomy[56] and the possibility of death from toxic megacolon,[49] from persistent colitis[55,60] or from complications of treatment.[58]

The typical sigmoidoscopic appearance includes an erythematous mucosa which may be friable or edematous, and numerous white or yellowish raised plaques less than 1 cm in diameter.[61,62] Histologic features of the rectosigmoid include the presence of a pseudomembrane, surface ulceration and mucosal inflammation.[61,62] These histologic features are identical to those seen in other cases of pseudomembranous colitis, including both those associated with administration of antibiotics and those attributable to other causes.[44] Barium enema examination of the colon shows extensive involvement of the colon with innumerable small plaques as described on sigmoidoscopy. These are slightly raised above the surface of the mucosa and are particularly well shown on air contrast studies.[62,63] Ulceration may or may not be prominent.[64] Discontinuation of clindamycin may result in cessation of symptoms in those patients who develop colitis while taking the drug. Otherwise, symptomatic treatment, if necessary including rectal and sometimes systemic corticosteroids, usually results in clinical improvement. Opiates, however, should probably be avoided.

The incidence of clindamycin-related colitis is unknown. The manufacturer suggests that "serious colitis probably occurs at an overall rate of between one in 50,000 and one in 100,000 uses of clindamycin" (Letter, The Upjohn Company, August 16, 1974). The number of cases reported in the literature and presented at meetings suggests that the actual number may be considerably greater than this. While the incidence of this illness following use of other antibiotics is also known, the syndrome appears to be considerably more common after use of the lincomycin group of drugs.

Conclusion

Clindamycin is clearly an effective antimicrobial agent. It is particularly useful as an alternative agent to penicillins and cephalosporins in infections due to Staphylococcus aureus and in the management of infections due to nonspore-forming anaerobic Gram-negative bacteria, particularly Bacteroides fragilis. As with any new drug, adverse effects become more apparent with more extensive use of the drug. Clindamycin has replaced chloramphenicol as the drug of choice in severe Bacteroidaceae infections because of the bone marrow toxicity of chloramphenicol. A review of the literature suggests that severe adverse reactions may not be uncommon with clindamycin. The indications for the use of this drug are quite narrow. Its use in treating mild infections, or severe infections for which drugs of proven efficacy and safety are also available, is to be deplored. Clinicians and radiologists should be familiar with the clinical features of clindamycin-related colitis, and a history of current or prior treatment with clindamycin should be elicited in the evaluation of patients with diarrhea.

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BOOK REVIEWS

THE WESTERN JOURNAL OF MEDICINE does not review all books sent to it by the publishers. A list of new books received is carried in the Advertising Section.

FUNCTIONAL ANATOMY OF THE CIRCULATION TO THE LOWER EXTREMITIES WITH COLOR ATLAS—Margaret C. Conrad, PhD, Associate Professor of Physiology, Medical University of South Carolina, Charleston. Year Book Medical Publishers, Inc., 35 East Wacker Drive, Chicago (60601), 1971. 190 pages, $22.00.

This small monograph was intended for students, and should provide a stimulating adjunct to basic science courses. One important regional circulation is discussed in detail, as an example of how structural, hemodynamic and neurohumoral control mechanisms interact to subserve functions peculiar to the tissues of the region, in this case, muscle and skin of the lower extremity. Temperature regulation and vascular responses to exercise and postural change are considered. A final section on pathologic conditions deals chiefly with diabetic and arteriosclerotic occlusive disease. Here is summarized the author's painstaking research, in which preoperative measurements of blood flow and skin temperature in gangrenous limbs were followed by detailed anatomic study of the vasculature after amputation. The pièce de résistance is a series of 31 plates showing plastic casts of blood vessels in normal and pathologic states. Particularly instructive and beautiful are the 3-dimensional images of vasa vasorum and the microcirculations of several tissues.

ELLEN BROWN, MD

* * *

NEONATOLOGY—Diseases of the Fetus and Infant—Edited by Richard E. Behrman, MD, Professor and Chairman, Department of Pediatrics, Columbia University College of Physicians and Surgeons; Director, Babies Hospital, The Children's Medical and Surgical Center of New York. The C. V. Mosby Company, 3301 Washington Blvd., St. Louis, MO (63103), 1973. 698 pages, 215 illustrations, including one color plate, $39.50.

In the past 2 years several textbooks of neonatal medicine have been published; among these *Neonatology—Diseases of the Fetus and Infant,* edited by Richard E. Behrman, is the most complete and useful. Its organization and chapter topics are orderly and reasonably complete. Following the first chapter, which deals briefly and succinctly with prenatal evaluation and monitoring of the feto-placental unit as well as the initial evaluation of the newborn, several chapters are concerned with neonatal emergencies, injuries, routine and special care. The remainder of the text is organized by organ system, and is devoted to consideration of the various diseases which affect the neonate. Most of these chapters are introduced by brief discussions of the embryology and physiology of the organ system. The chapter on the cardiovascular system is excellent, with commendable presentations of clinical and laboratory cardiac evaluation, and concise yet complete coverage of the various congenital and acquired disorders.

On the negative side, there are several instances of failure to clearly indicate which modes of therapy have been scientifically validated and which are merely preferences based on anecdotal experiences. In contrast, in the respiratory chapter, it seems excessively cautious to state that the recommendation of continuous positive airway pressure for routine therapy of hyaline membrane disease must await further study. Also, as with many first printings, this volume has some significant errors. For example, the formula for the calculation of pulmonary resistance is incorrectly stated, and the dosage of intravenous Isuprel as recommended in the Appendix is one thousand times the correct dose.

However, the above shortcomings are minor and *Neonatology—Diseases of the Fetus and Infant,* overall receives high marks particularly for its organization and emphasis on pathophysiology, although it is hoped that in the next edition there will be more complete documentation of the efficacy of the forms of treatment advocated.

WILLIAM H. TOOLEY, MD

* * *

ANTICIPATORY GRIEF—Edited by Bernard Schoenberg, MD, Arthur C. Carr, PhD, Austin H. Kutscher, DDS, David Peretz, MD, and Ivan K. Goldberg, MD. Columbia University Press, 562 West 113th Street, New York City (10025), 1974. 381 pages, $12.50.

This volume explores anticipatory grief as the phenomenon of bereavement which takes place prior to the actual loss. It is to be clearly distinguished from the grief which occurs at, or after the loss, and obviously, it has a finite end-point as a result of this consideration. It is obviously of great value to practicing physicians to be aware of these grief reactions, not only in terms of the care of the terminally ill patient himself, now anticipating his end-state, but also his family, who likewise anticipated. In addition to that, the anticipated loss is experienced by the relatives, physicians, social workers, clergymen, and friends. The studies in this book offer the practicing physician the opportunity to grow a sophistication about this phenomenon, and obviously offers him then, an opportunity to identify those high risk individuals and to institute proper management which may help forestall the psychological and physical illness in the bereaved.

This book is one of a series from the Foundation of Thanatology, an Institute representing a new sub-specialty of medicine involved in scientific and humanistic inquiries and the application of the knowledge derived therefrom to the subjects of the psychological aspects of dying, reactions to loss, death and grief, and recovery from bereavement. The Foundation's orientation is toward a more effective and humane management and treatment of the dying patient and his bereaved family members. This particular volume contains forty-one papers arranged in five major sub-sections: (1) Introductory Concepts, (2) Clinical Aspects, (3) Childhood Illness, (4) The Health Profession, (5) The Management of Anticipatory Grief, (6) Pastoral Aspects. The authors of these papers widely represent the clinical fields involved: There are 19 physicians, mostly psychiatrists and pediatricians, 6 social workers, 13 social scientists, 3 nurses, 1 dentist, and 8 pastoral counselors. All of them are associated with academic and clinical institutions and show evidence of deep personal and clinical involvement. The volume has the problem of all collections of this nature, namely there is a great deal of redundancy, since each paper introduces the subject and the conclusions generalize toward the major field. However, it has the advantages, that a particularly interested individual can immediately go to the paper most relevant to his inquiry for example, "Anticipatory Grief in a Cancer Hospital"; "Parents of Fatally Ill Children in a

Parent Group"; "Social Workers' Responsibility"; "Drug Ingestion and Suicide During Anticipatory Grief." Probably the most widely quoted bibliographical reference is of the San Francisco team of Glaser and Strauss. Their book, *The Awareness of Dying,* published by Aldine, in Chicago, is a very thorough, complete and intimate doctrine of the problem.

The primary topic of grief which would include depression, disillusionment, giving up, etc., as a reaction pattern, is of increasing importance in theoretical clinical medicine for it is being demonstrated in many excellent clinical reviews, that those people who tend to give up, experience the onset of illness forms, complications in illnesses already present, a greater mortality in the complicated treatment regimen such as transplantation. It is important for all physicians to increase their sophistication about these phenomena since their clinical presence can no longer be viewed as incidental.

H. HARRISON SADLER, MD

* * *

SURGICAL TREATMENT OF HEAD AND NECK TUMORS—Edited by Jorge Fairbanks Barbosa, MD, Chief, Group of Surgery, Central Institute of the Associaçao Paulista de Combate ao Cancer, Corresponding Fellow of the Society of Head and Neck Surgeons and of the American Academy of Facial Plastic and Reconstructive Surgery. Grune & Stratton, Inc., 111 Fifth Avenue, New York City (10003), 1974. 311 pages, $35.00.

This 311-page, well illustrated text is an exposition of the technical approach to management of tumors of the head and neck. Dr. Barbosa and his colleagues present liberally illustrated, step-by-step fashion, their own approach to the management of these disorders. The illustrations are semirealistic drawings that manage to clearly demonstrate the anatomical landmarks and important structures. They add great pleasure to the reading of this book.

The authors make no effort to provide an exhaustive treatise of techniques, but rather strive to share their own step by step detailed technique for adequate removal of tumors of each of the regions within the head and neck. Their techniques are rather standard and readers looking for innovation will be disappointed. Most interesting is the insight into the methodology and techniques utilized by our South American colleagues.

The appeal of this book should be widespread including otolaryngologists, head and neck surgeons, plastic surgeons, maxillofacial surgeons, oncologists, and others interested in the management of tumors of this area.

PAUL H. WARD, MD

* * *

PSYCHIATRY IN PRIMARY CARE—Remi J. Cadoret, MD, Professor of Psychiatry, Departments of Psychiatry and Family Practice, School of Medicine, University of Iowa; and Lucy J. King, MD, Associate Professor, Department of Psychiatry, School of Medicine, Washington University, St. Louis. The C. V. Mosby Company, Publishers, 3301 Washington Boulevard, St. Louis, MO (63103), 1974. 339 pages, $12.95.

Recognizing that the majority of patients that seek help from the practitioner have primary or complicating psychiatric problems, this text is written for physicians engaged in primary care. It is a practical compendium designed to teach the family practitioner in a manner consistent with the way he thinks and practices. Rather than exploring possible causes of mental illness the authors approach the problem by describing the basic syndromes. The descriptions are oriented to manifest behavior and avoid the intrapsychic and sociocultural theory common to psychiatric text books.

The syndromes described include all of the major psychiatric disorders—affective disorders, schizophrenic syndromes, alcoholism and drug abuse, sexual variants, and organic brain syndromes. A series of tables summarize the information necessary to identify a syndrome. In schematic form, the primary care physician is encouraged to take a thorough history of the presenting problem, a personal and social history, a family history, and to do a mental status. A large chart for the eleven syndromes organizes information under these four categories. Additional tables teach the physician how to do a personal and social history, a family history and a mental status. A transcribed sample interview demonstrates that this information can be gathered rapidly. The major strength of the book is this approach to differential diagnoses.

The section on treatment includes chapters on psychotherapy, medication, ECT, and psychiatric emergencies. Although there is one chapter describing the theoretical background of psychotherapy, a second is designed to offer practical suggestions. The chapter on medication is disappointing. In eight pages there is a skimpy outline which pays too little attention to the side effects associated with medication and which does not sufficiently stress the need for individualizing psychoactive medication in each case.

All in all, a useful volume and one which is recommended to the audience for whom it was obviously written—the primary care physician.

DONALD G. LANGSLEY, MD

* * *

GENERAL OPHTHALMOLOGY—Seventh Edition—Daniel Vaughan, MD, Associate Clinical Professor of Ophthalmology, University of California, San Francisco, School of Medicine; and Taylor Asbury, MD, Professor and Director, Department of Ophthalmology, College of Medicine, University of Cincinnati. Lange Medical Publications, Drawer L, Los Altos, CA (94022), 1974. 334 pages, $9.50.

Vaughan and Asbury's textbook of *General Ophthalmology* for medical students and general physicians is an exceptionally useful volume. The authors' desire to remain current is reflected in the fact that this most recent effort is the seventh edition of a very popular work, whose first edition appeared as recently as 1958. Further evidence of the current nature of this book is obtained by noting the topics which are not only currently important in ophthalmology, but relevant to the audience for whom this book is intended. For instance, advances in neuroradiology, ultrasonography, medical therapeutics, and ocular surgery are well covered. Although relatively inexpensive, the book is skillfully and generously illustrated with drawings and photographs which are not only clear, but are particularly helpful to the intended audience. The organization of material into chapters, and the indexing are logical and cohesive. The book is not only thoroughly readable but is assembled in such a way as to make quick consultation regarding specific questions easy. The appendices, of which there are three, include one on commonly used eye medications and another on ophthalmoscopic examination, which again are particularly useful for the medical student or practicing general physician.

This book is to be recommended without reservation.

ROBERT S. HEPLER, MD

Prospective Medicine . . .

The 83rd Annual Meeting

of the

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JULY 30-AUGUST 2, 1975

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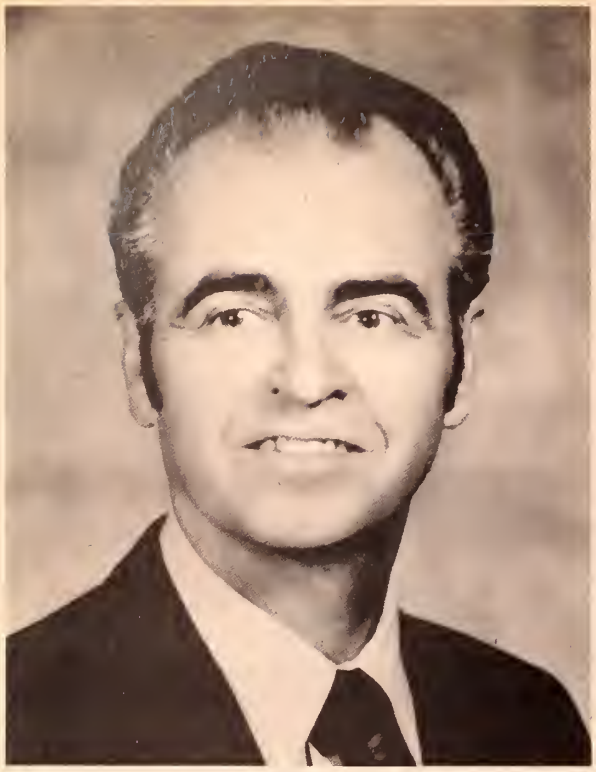

I am very pleased to invite you to attend the 83rd annual meeting of the Idaho Medical Association at beautiful Sun Valley, July 30 through August 2, 1975.

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R. GEORGE WOLFF, MD
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RONALD G. BLANKENBAKER, MD

THE FACULTY . . .

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Director of Family Practice Education, Assistant Professor of Family Practice,
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THE TOPICS . . .

- KEYNOTE: Prospective Medicine
- Charlie Brown's Approach to the Problem Oriented Records
- Planning Ahead for Problems in Pregnancy
- To Drink or Not to Drink
- Precursors of Cancer
- Reduction of Motor Vehicle Deaths
- Polyps in Proctology—Up the Down Tube
- Prevention of Cancer of the Breast
- Reduced Risks of Cancer of the Uterus
- Prospecting Coronary Heart Disease
- Natural History of Depression
- Fats, Pressures and Sedentaries
- Obesity and Diabetes
- Cigarettes as a Pre-Cursor
- Preventive Psychiatry

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in memoriam

ARNOLD, HOMER J., Los Angeles. Died April 2, 1975 of cancer, age 82. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1915. Licensed in California in 1926. MD degree from California College of Medicine, 1962. Dr. Arnold was a member of the Los Angeles County Medical Association.

BUTTERFIELD, ALTON D., Loma Linda. Died March 20, 1975 in Loma Linda, aged 87. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1917. Licensed in California in 1917. Dr. Butterfield was a member of the San Bernardino County Medical Society.

CARLETON, EDWARD H., Solvang. Died April 19, 1975, aged 70. Graduate of the University of Louisville School of Medicine, 1932. Licensed in California in 1967. Dr. Carleton was a member of the Santa Barbara County Medical Society.

CARMACK, CHARLES E., San Bernardino. Died April 17, 1975 in San Bernardino of heart disease, aged 58. Graduate of Baylor University College of Medicine, Houston, 1940. Licensed in California in 1941. Dr. Carmack was a member of the San Bernardino County Medical Society.

DUNCAN, JAMES T., Yucca Valley. Died April 5, 1975 in Los Angeles of heart disease, aged 70. Graduate of Western Reserve University School of Medicine, Cleveland, 1933. Licensed in California in 1945. Dr. Duncan was a retired member of the Kern County Medical Society.

GARDNER, HENRY L., San Francisco. Died April 8, 1975 in Walnut Creek, aged 79. Graduate of Vanderbilt University School of Medicine, Nashville, 1923. Licensed in California in 1924. Dr. Gardner was a member of the San Francisco Medical Society.

HALL, THOMAS G., San Francisco. Died March 29, 1975, aged 84. Graduate of St. Louis University School of Medicine, 1923. Licensed in California in 1933. Dr. Hall was a member of the San Francisco Medical Society.

HARRIS, MARVIN SAUL, Los Angeles. Died April 6, 1975 in Canoga Park of Alzheimer's disease, aged 69. Graduate of the University of Buffalo School of Medicine, 1928. Licensed in California in 1929. Dr. Harris was a member of the Los Angeles County Medical Association.

HESTON, LAURENCE L., Aptos. Died November 15, 1974 of multiple myeloma, aged 61. Graduate of the University of California Medical School, Berkeley-San Francisco, 1939. Licensed in California in 1939. Dr. Heston was a retired member of the San Joaquin County Medical Society.

HOGG, CHARLES E., Torrance. Died March 24, 1975, aged 41. Graduate of the George Washington University School of Medicine, Washington, DC, 1960. Licensed in California in 1969. Dr. Hogg was a member of the Los Angeles Medical Association.

KUMMER, JEROME M., Santa Monica. Died March 20, 1975 in Meriden, Connecticut, aged 54. Graduate of New York Medical College, 1944. Licensed in California in 1947. Dr. Kummer was a member of the Los Angeles County Medical Association.

ROLLAND, WARD MILLER, Los Angeles. Died April 5, 1975 of heart disease, aged 70. Graduate of the University of Michigan Medical School, Ann Arbor, 1928. Licensed in California in 1931. Dr. Rolland was a member of the Los Angeles County Medical Association.

SAUNDERS, CECIL ALLEN, San Francisco. Died April 6, 1975 in Sonoma, aged 78. Graduate of College of Physicians and Surgeons, Medical Department, University of Southern California, 1919. Licensed in California in 1919. Dr. Saunders was a member of the San Francisco Medical Society.

SCHWARTZ, JOSEPH ATLAS, Los Angeles. Died March 21, 1975 in Los Angeles of heart disease, aged 64. Graduate of New York University College of Medicine, 1934. Licensed in California in 1950. Dr. Schwartz was a member of the Los Angeles County Medical Association.

SIMONDS, SHERBORNE B., Alhambra. Died March 8, 1975, aged 54. Graduate of Cornell University Medical College, New York, 1945. Licensed in California in 1948. Dr. Simonds was a member of the Los Angeles County Medical Association.

SOLOMON, JOSEPH C., San Francisco. Died March 29, 1975 in San Francisco, aged 71. Graduate of Syracuse University College of Medicine, 1927. Licensed in California in 1940. Dr. Solomon was a member of the San Francisco Medical Society.

WEYRAUCH, HELEN B., San Francisco. Died April 26, 1975 in San Francisco, aged 66. Graduate of Johns Hopkins University School of Medicine, Baltimore, 1934. Licensed in California in 1937. Dr. Weyrauch was a past secretary of the California Medical Association and a member of the San Francisco Medical Society.

WILLIAMS, ERNEST W., JR., Bakersfield. Died March 30, 1975 in Bakersfield, aged 62. Graduate of Meharry Medical College, Nashville, 1941. Licensed in California in 1947. Dr. Williams was a member of the Kern County Medical Society.

YAMADA, PAUL M., Los Altos. Died March 11, 1975 in Mountain View, aged 67. Graduate of the University of Oregon Medical School, Portland, 1956. Licensed in California in 1957. Dr. Yamada was a member of the Santa Clara County Medical Society.

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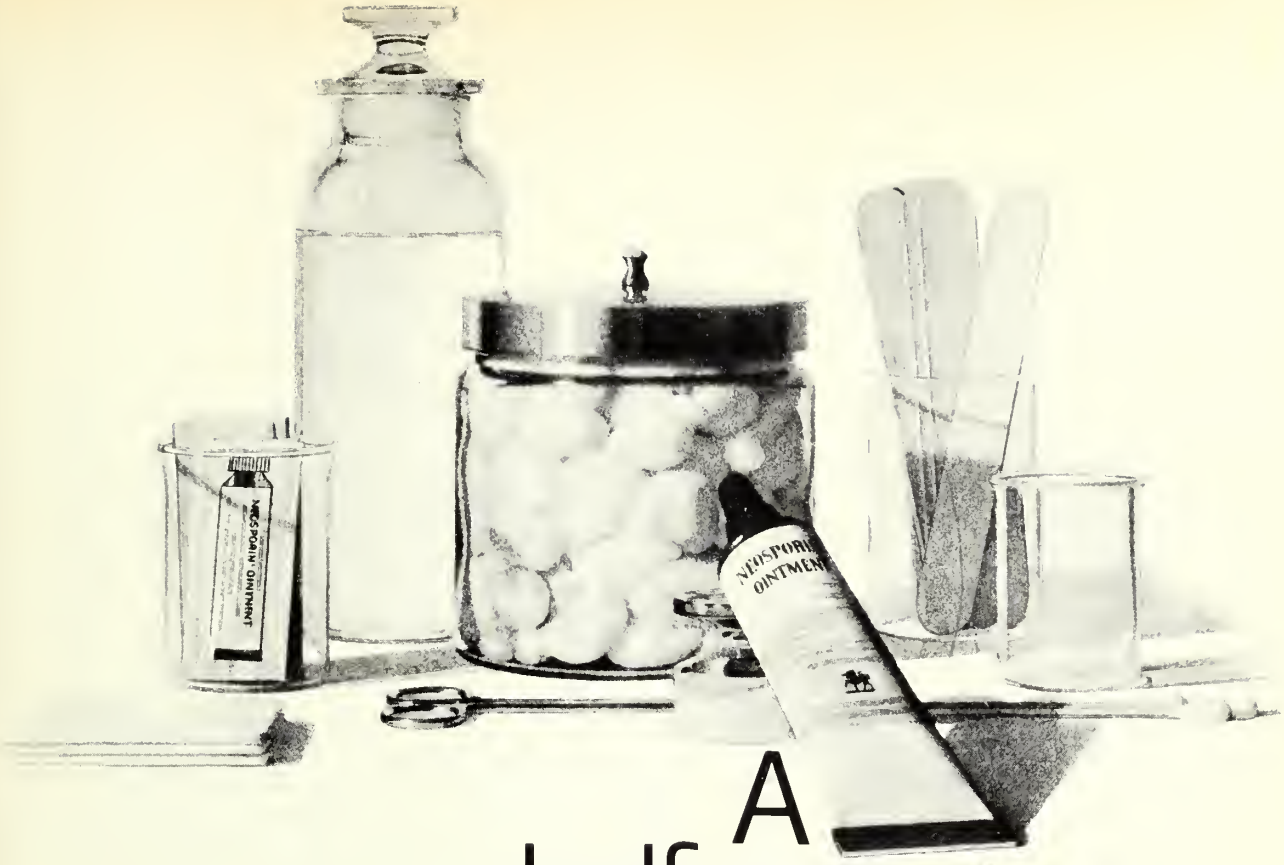

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In tubes of 1 oz and 1/2 oz and 1/32 oz (approx.) foil packets.

INDICATIONS: *Therapeutically,* used as an adjunct to appropriate systemic therapy for topical infections, primary or secondary, due to susceptible organisms, as in: • infected burns, skin grafts, surgical incisions, otitis externa • primary pyodermas (impetigo, ecthyma, sycosis vulgaris, paronychia) • secondarily infected dermatoses (eczema, herpes, and seborrheic dermatitis) • traumatic lesions, inflamed or suppurating as a result of bacterial infection.
Prophylactically, the ointment may be used to prevent bacterial contamination in burns, skin grafts, incisions, and other clean lesions. For abrasions, minor cuts and wounds accidentally incurred, its use may prevent the development of infection and permit wound healing.

CONTRAINDICATIONS: Not for use in the eyes or external ear canal if the eardrum is perforated. This product is contraindicated in those individuals who have shown hypersensitivity to any of the components.

WARNING: Because of the potential hazard of nephrotoxicity and ototoxicity due to neomycin, care should be exercised when using this product in treating extensive burns, trophic ulceration and other extensive conditions where absorption of neomycin is possible. In burns where more than 20 percent of the body surface is affected, especially if the patient has impaired renal function or is receiving other aminoglycoside antibiotics concurrently, not more than one application a day is recommended.

PRECAUTIONS: As with other antibacterial preparations, prolonged use may result in overgrowth of nonsusceptible organisms, including fungi. Appropriate measures should be taken if this occurs.

ADVERSE REACTIONS: Neomycin is a not uncommon cutaneous sensitizer. Articles in the current literature indicate an increase in the prevalence of persons allergic to neomycin. Ototoxicity and nephrotoxicity have been reported (see Warning section).

Complete literature available on request from Professional Services Dept. PML.

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If he could only sleep standing up ...any antacid might do.

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*Higgs, R. H., Smyth, R. D., and Castell, D. O., Gastric Alkalinization—Effect on Lower-Esophageal-Sphincter Pressure and Serum Gastrin, *The New Engl. J. of Med.*, 291, 486-490, 1974.

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For more than thirty years PREMARIN (Conjugated Estrogens Tablets, U.S.P.) has been prepared with natural equine estrogens exclusively—without synthetic estrogen supplements. For more than thirty years it has provided the complete estrogen complex in the proportions found in its natural source. And for more than thirty years PREMARIN has enjoyed an unparalleled record of clinical efficacy and acceptance.

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BRIEF SUMMARY
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(Conjugated Estrogens Tablets, U.S.P.)

Indications: Based on a review of PREMARIN Tablets by the National Academy of Sciences-National Research Council and/or other information, FDA has classified the indications for use as follows:
Effective: As replacement therapy for naturally occurring or surgically induced estrogen deficiency states associated with: the climacteric, including the menopausal syndrome and postmenopause; senile vaginitis and kraurosis vulvae, with or without pruritus.
"Probably" effective: For estrogen deficiency-induced osteoporosis, and only when used in conjunction with other important therapeutic measures such as diet, calcium, physiotherapy, and good general health-promoting measures. Final classification of this indication requires further investigation.

Contraindications: Short acting estrogens are contraindicated in patients with (1) markedly impaired liver function; (2) known or suspected carcinoma of the breast, except those cases of progressing disease not amenable to surgery or irradiation occurring in women who are at least 5 years postmenopausal; (3) known or suspected estrogen-dependent neoplasia, such as carcinoma of the endometrium; (4) thromboembolic disorders, thrombophlebitis, cerebral embolism, or in patients with a past history of these conditions; (5) undiagnosed abnormal genital bleeding.
Warnings: Estrogen therapy should not be given to women with recurrent chronic mastitis or abnormal mammograms except, if in the opinion of the physician, it is warranted despite the possibility of aggravation of the mastitis or stimulation of undiagnosed estrogen-dependent neoplasia.

The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, retinal thrombosis, cerebral embolism and pulmonary embolism). If these occur or are suspected, estrogen therapy should be discontinued immediately.

Estrogens may be excreted in the mother's milk and an estrogenic effect upon the infant has been described. The long range effect on the nursing infant cannot be determined at this time.

Hypercalcemia may occur in as many as 15 percent of breast cancer patients with metastases, and this usually indicates progression of bone metastases. This occurrence depends neither on dose nor on immobilization. In the presence of progression of the cancer or hypercalcemia, estrogen administration should be stopped.

A statistically significant association has been reported between maternal ingestion of diethylstilbestrol during pregnancy and the occurrence of vaginal carcinoma in the offspring. This occurred with the use of diethylstilbestrol for the treatment of threatened abortion or high risk pregnancies. Whether or not such an association is applicable to all estrogens is not known at this time. In view of this finding, however, the use of any estrogen in pregnancy is not recommended.

Failure to control abnormal uterine bleeding or unexpected recurrence is an indication for curettage.
Precautions: As with all short acting estrogens, the following precautions should be observed:

A complete pretreatment physical examination should be performed with special reference to pelvic and breast examinations.

To avoid prolonged stimulation of the endometrium and breasts in climacteric or hypogonadal women, estrogens should be administered cyclically (3 week regimen with 1 week rest period—withdrawal bleeding may occur during rest period).

Because of individual variation in endogenous estrogen production, relative overdosage may occur which could cause undesirable effects such as abnormal or excessive uterine bleeding, mastodynia and edema.

Because of salt and water retention associated with estrogenic anabolic activity, estrogens should be used with caution in patients with epilepsy, migraine, asthma, cardiac, or renal disease.

If unexplained or excessive vaginal bleeding should occur, reexamination should be made for organic pathology.

Pre-existing uterine fibromyomata may increase in size while using estrogens; therefore, patients should be examined at regular intervals while receiving estrogenic therapy.

The pathologist should be advised of estrogen therapy when relevant specimens are submitted.

Because of their effects on epiphyseal closure, estrogens should be used judiciously in young patients in whom bone growth is incomplete.

Prolonged high dosages of estrogens will inhibit anterior pituitary functions. This should be borne in mind when treating patients in whom fertility is desired.

The age of the patient constitutes no absolute limiting factor, although treatment with estrogens may mask the onset of the climacteric.

Certain liver and endocrine function tests may be affected by exogenous estrogen administration. If test results are abnormal in a patient taking estrogen, they should be repeated after estrogen has been withdrawn for one cycle.
Adverse Reactions: The following adverse reactions have been reported associated with short acting estrogen administration:
nausea, vomiting, anorexia
gastrointestinal symptoms such as abdominal cramps and bloating
breakthrough bleeding, spotting, unusually heavy withdrawal bleeding (See DOSAGE AND ADMINISTRATION)
breast tenderness and enlargement
reactivation of endometriosis
possible diminution of lactation when given immediately postpartum
loss of libido and gynecomastia in males
edema
aggravation of migraine headaches
change in body weight (increase, decrease)
headache
allergic rash
hepatic cutaneous porphyria becoming manifest
Dosage and Administration: PREMARIN should be administered cyclically (3 weeks of daily estrogen and 1 week off) for all indications except selected cases of carcinoma and prevention of postpartum breast engorgement.

Menopausal Syndrome—1.25 mg. daily, cyclically. Adjust dosage upward or downward according to severity of symptoms and response of the patient. For maintenance, adjust dosage to lowest level that will provide effective control.

If the patient has not menstruated within the last two months or more, cyclic administration is started arbitrarily. If the patient is menstruating, cyclic administration is started on day 5 of bleeding. If breakthrough bleeding (bleeding or spotting during estrogen therapy) occurs, increase estrogen dosage as needed to stop bleeding. In the following cycle, employ the dosage level used to stop breakthrough bleeding in the previous cycle. In subsequent cycles, the estrogen dosage is gradually reduced to the lowest level which will maintain the patient symptom-free.

Postmenopause—as a protective measure against estrogen deficiency-induced degenerative changes (*e.g.* osteoporosis, atrophic vaginitis, kraurosis vulvae)—0.3 mg. to 1.25 mg. daily and cyclically. Adjust dosage to lowest effective level.

Osteoporosis (to retard progression)—usual dosage 1.25 mg. daily and cyclically.

Senile Vaginitis, Kraurosis Vulvae with or without Pruritus—0.3 mg. to 1.25 mg. or more daily, depending upon the tissue response of the individual patient. Administer cyclically.
How Supplied: PREMARIN (Conjugated Estrogens Tablets, U.S.P.)

No. 865—Each *purple* tablet contains 2.5 mg., in bottles of 100 and 1,000.

No. 866—Each *yellow* tablet contains 1.25 mg., in bottles of 100 and 1,000. Also in unit dose package of 100.

No. 867—Each *red* tablet contains 0.625 mg., in bottles of 100 and 1,000.

No. 868—Each *green* tablet contains 0.3 mg., in bottles of 100 and 1,000. 7352

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to help treat what you often find:
obvious moderate to severe anxiety
with a less obvious underlying depression

TRIAVIL®

containing perphenazine and amitriptyline HCl

a tranquilizer–antidepressant

"...and she'd jump every time the phone rang."

"All right, I agree, she was obviously very anxious...you said she hadn't been sleeping...."

"She felt *tired enough* to sleep... not relaxed enough...food, too... she's too nervous to eat...says she *can't* relax...afraid there's something very wrong with her."

"...that's a good place to start! Did you find anything wrong with her?"

Treatment with TRIAVIL—a balanced view.

Tablets TRIAVIL are available in four different combinations affording flexibility and individualized dosage adjustment. Close supervision of patients is essential until satisfactory remission has taken place. Since suicide is a possibility in any depressive illness, patients should not have easy access to large quantities of the drug. The drug may impair alertness and potentiate the response to alcohol. It should not be used during the acute recovery phase following myocardial infarction or given to patients who have received an MAOI within two weeks. TRIAVIL should be used with caution in glaucoma and in patients prone to urinary retention. It is contraindicated in CNS depression and in the presence of evidence of bone marrow depression.

MSD MERCK SHARP & DOHME For a brief summary of prescribing information, please turn to the following page.

"Not a thing... negative... nothing organically wrong. Still has a fair list of somatic complaints. I've tried to reassure her... to let her talk... to help her sort things out. She's been in to see me a number of times."

"...what about medication?"

"Just what I was coming to... I've had her on tranquilizers. And *that's* what puzzles me. I'm not getting the response I hoped for. She's no better... perhaps a little worse. It's sad to see."

"...I think *'sad'* may be what you're not seeing! You know, this sounds like another case where the *anxiety* is so clear and pervasive we tend to overlook the depressive part of the picture. I'm not sure that we shouldn't almost always think of anxiety *with* depression... not anxiety alone. Take another look at your records... talk to her some more. If you decide she's depressed, I think you might want to consider TRIAVIL.... It can help relieve her entire symptom complex... control the anxiety... while at the same time treat the depression."

TRIAVIL®

containing perphenazine and amitriptyline HCl

a tranquilizer–antidepressant

to help treat what you often find: obvious moderate to severe anxiety with a less obvious underlying depression

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TRIAVIL® 4-25: Each tablet contains
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CONTRAINDICATIONS: Central nervous system depression from drugs (barbiturates, alcohol, narcotics, analgesics, antihistamines); bone marrow depression; known hypersensitivity to phenothiazines or amitriptyline. Do not give concomitantly with MAOI drugs because hyperpyretic crises, severe convulsions, and deaths have occurred from such combinations. Allow minimum of 14 days between therapies, then initiate therapy with TRIAVIL cautiously, with gradual increase in dosage until optimum response is achieved. Not recommended for use during acute recovery phase following myocardial infarction.

WARNINGS: TRIAVIL should not be given with guanethidine or similarly acting compounds. Use cautiously in patients with history of urinary retention, angle-closure glaucoma, increased intraocular pressure, or convulsive disorders. In patients with angle-closure glaucoma, even average doses may precipitate an attack. Patients with cardiovascular disorders should be watched closely. Tricyclic antidepressants, including amitriptyline HCl, particularly in high doses, have been reported to produce arrhythmias, sinus tachycardia, and prolongation of conduction time. Myocardial infarction and stroke have been reported with tricyclic antidepressant drugs. Close supervision is required for hyperthyroid patients or those receiving thyroid medication. Caution patients performing hazardous tasks, such as operating machinery or driving motor vehicles, that drug may impair mental and/or physical abilities. Not recommended in children or during pregnancy.

PRECAUTIONS: Suicide is a possibility in depressed patients and may remain until significant remission occurs. Such patients should not have access to large quantities of this drug.

Perphenazine: Should not be used indiscriminately. Use with caution in patients who have previously exhibited severe adverse reactions to other phenothiazines. Likelihood of untoward actions is greater with high doses. Closely supervise with any dosage. The antiemetic effect of perphenazine may obscure signs of toxicity due to overdosage of other drugs or make more difficult the diagnosis of disorders such as brain tumor or intestinal obstruction. A significant, not otherwise explained, rise in body temperature may suggest individual intolerance to perphenazine, in which case discontinue.

If hypotension develops, epinephrine should not be employed, as its action is blocked and partially reversed by perphenazine. Phenothiazines may potentiate the action of central nervous system depressants (opiates, analgesics, antihistamines, barbiturates, alcohol) and atropine. In concurrent therapy with any of these, TRIAVIL should be given in reduced dosage. May also potentiate the action of heat and phosphorous insecticides.

Amitriptyline: In manic-depressive psychosis, depressed patients may experience a shift toward the manic phase if they are treated with an antidepressant. Patients with paranoid symptomatology may have an exaggeration of such symptoms. The tranquilizing effect of TRIAVIL seems to reduce the likelihood of this effect. When amitriptyline HCl is given with anticholinergic agents or sympathomimetic drugs, including epinephrine combined with local anesthetics, close supervision and careful adjustment of dosages are required.

Caution is advised if patients receive large doses of ethchlorvynol concurrently. Transient delirium has been reported in patients who were treated with 1 g of ethchlorvynol and 75-150 mg of amitriptyline HCl.

Amitriptyline HCl may enhance the response to alcohol and the effects of barbiturates and other CNS depressants.

Concurrent administration of amitriptyline HCl and electroshock therapy may increase the hazards associated with such therapy. Such treatment should be limited to patients for whom it is essential. Discontinue several days before elective surgery if possible. Elevation and lowering of blood sugar levels have both been reported.

ADVERSE REACTIONS: Similar to those reported with either constituent alone.

Perphenazine: Side effects may be any of those reported with phenothiazine drugs: extrapyramidal symptoms (opisthotonus, oculogyric crisis, hyperreflexia, dystonia, akathisia, acute dyskinesia, ataxia, parkinsonism) can usually be controlled by the concomitant use of effective antiparkinsonian drugs and/or by reduction in dosage, but sometimes persist after discontinuation of the phenothiazine.

Tardive dyskinesia may appear in some patients on long-term therapy or may occur after drug therapy with phenothiazines and related agents has been discontinued. The risk appears to be greater in elderly patients on high-dose therapy, especially females. Symptoms are persistent and in some patients appear to be irreversible. The syndrome is characterized by rhythmical involuntary movements of the tongue, face, mouth, or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Involuntary movements of the extremities sometimes occur. There is no known treatment for tardive dyskinesia; antiparkinsonism agents usually do not alleviate the symptoms. It is advised that all antipsychotic agents be discontinued if the above symptoms appear. If treatment is reinstituted, or dosage of the particular drug increased, or another drug substituted, the syndrome may be masked. It has been suggested that fine vermicular movements of the tongue may be an early sign of the syndrome, and that the full-blown syndrome may not develop if medication is stopped when lingual vermiculation appears.

Other side effects are skin disorders (photosensitivity, itching, erythema, urticaria, eczema, up to exfoliative dermatitis); other allergic reactions (asthma, laryngeal edema, angioneurotic edema, anaphylactoid reactions); peripheral edema; reversed epinephrine effect; hyperglycemia; endocrine disturbances (lactation, galactorrhea, gynecomastia, disturbances of menstrual cycle); altered cerebrospinal fluid proteins; paradoxical excitement; hypertension, hypotension, tachycardia, and ECG abnormalities (quinidine-like effect); reactivation of psychotic processes; catatonic-like states; autonomic reactions, such as dry mouth or salivation, headache, anorexia, nausea, vomiting, constipation, obstipation, urinary frequency or incontinence, blurred vision, nasal congestion, and a change in pulse rate; hypnotic effects; pigmentary retinopathy; corneal and lenticular pigmentation; occasional lassitude, muscle weakness, mild insomnia. Other adverse reactions reported with various phenothiazine compounds include blood dyscrasias (pancytopenia, thrombocytopenic purpura, leukopenia, agranulocytosis, eosinophilia); liver damage (jaundice, biliary stasis); grand mal convulsions; cerebral edema; polyphagia; photophobia; skin pigmentation; and failure of ejaculation.

Amitriptyline: Note: Listing includes a few reactions not reported for this drug, but which have occurred with other pharmacologically similar tricyclic antidepressant drugs. *Cardiovascular:* Hypotension; hypertension; tachycardia; palpitation; myocardial infarction; arrhythmias; heart block; stroke. *CNS and Neuromuscular:* Confusional states; disturbed concentration; disorientation; delusions; hallucinations; excitement; anxiety; restlessness; insomnia; nightmares; numbness, tingling, and paresthesias of the extremities; peripheral neuropathy; incoordination; ataxia; tremors; seizures; alteration in EEG patterns; extrapyramidal symptoms; tinnitus. *Anticholinergic:* Dry mouth; blurred vision; disturbance of accommodation; constipation; paralytic ileus; urinary retention; dilatation of urinary tract. *Allergic:* Skin rash; urticaria; photosensitization; edema of face and tongue. *Hematologic:* Bone marrow depression including agranulocytosis; leukopenia; eosinophilia; purpura; thrombocytopenia. *Gastrointestinal:* Nausea; epigastric distress; vomiting; anorexia; stomatitis; peculiar taste; diarrhea; parotid swelling; black tongue. *Endocrine:* Testicular swelling and gynecomastia in the male; breast enlargement and galactorrhea in the female; increased or decreased libido; elevated or lowered blood sugar levels. *Other:* Dizziness, weakness; fatigue; headache; weight gain or loss; increased perspiration; urinary frequency; mydriasis; drowsiness; jaundice; alopecia. *Withdrawal Symptoms:* Abrupt cessation after prolonged administration may produce nausea, headache, and malaise. These are not indicative of addiction.

OVERDOSAGE: All patients suspected of having taken an overdosage should be admitted to a hospital as soon as possible. Treatment is symptomatic and supportive. However, the intravenous administration of 1-3 mg of physostigmine salicylate has been reported to reverse the symptoms of tricyclic antidepressant poisoning. On this basis, in severe overdosage with perphenazine-amitriptyline combinations, symptomatic treatment of central anticholinergic effects with physostigmine salicylate should be considered.

For more detailed information, consult your MSD Representative or see full Prescribing Information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, Pa 19486.

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(Continued on Page 32)

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(Continued from Page 31)

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(Continued on Page 38)

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COMMITTEE ON CONTINUING MEDICAL EDUCATION

THIS BULLETIN of information regarding continuing education programs and meetings of various medical organizations in **California and Hawaii** is supplied by the Committee on Continuing Medical Education of the California Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Committee on Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103; or phone (415) 777-2000. Note: Please see **California Medicine**, Vol. 117, No. 4, October, 1972 issue for a list of organizations approved for Category I Credit toward the CMA Certificate in Continuing Medical Education.

CANCER

August 21-22—**Multidisciplinary Approach to Cancer Treatment.** UCSF at Children's Hospital, San Francisco. Thursday-Friday.

MEDICINE

July 21-24—**Primary Care Dermatology.** STAN. Monday-Thursday.

August 2—**Hypoglycemia: What It Is and Isn't.** UCLA. Saturday.

August 13-17—**Advanced Seminar in Dermatology.** UCI at Newporter Inn, Newport Beach. Wednesday-Sunday.

September 18-June—**Review and Update in Surgery, Pediatrics, Ob-Gyn and Internal Medicine.** See Surgery, September 18-June.

September 19-20—**For the Physician in Private Practice: Strategies for Managing Hypertension.** PMC at St. Francis Hotel, San Francisco. Friday-Saturday. 18 hrs. $25.

September 27-28—**Workshop in Dermatologic Surgery.** UCSF. Saturday-Sunday.

OBSTETRICS AND GYNECOLOGY

September 18-June—**Review and Update in Surgery, Pediatrics, Ob-Gyn and Internal Medicine.** See Surgery, September 18.

September 25-27—**Fall Symposium in Obstetrics and Gynecology—Oncology, Endocrinology and Infertility.** UCSF at Stanford Court Hotel, San Francisco. Thursday-Saturday.

September 27-October 4—**Workshops in Gynecologic Oncology, High Risk Pregnancy and Endocrinology-Infertility.** UCSF at Maui, Hawaii. One week.

PEDIATRICS

June 24-28—**National Society for Autistic Children.** See Psychiatry, June 24-28.

July 1-3—**Thirty Grams of Prevention—Annual Pediatric Seminar.** Children's Hospital and Health Center, San Diego, at Hotel del Coronado, Coronado. Tuesday-Thursday. 16 hrs. $30. Contact: Mrs. Franci Perkins, Sec. to Med. Dir., Children's Hospital and Health Center, 8001 Frost St., San Diego 92123. (714) 277-5808, ext. 351.

September 18-June—**Review and Update in Surgery, Pediatrics, Ob-Gyn and Internal Medicine.** See Surgery, September 18.

September 24-25—**Brennemann Memorial Lectures—32nd Annual.** Los Angeles Pediatric Society at Sportsmen's Lodge, North Hollywood. Wednesday-Thursday. Contact: Mrs. Eve Black, Exec. Sec., P.O. Box 2022, Inglewood 90305. (213) 757-1198.

PSYCHIATRY

June 23-27—**Comparative Psychotherapies.** USC at The Waystation, Lake Tahoe. Monday-Friday. 21 hrs. $150. Contact: Donald H. Naftulin, MD, Dir., Cont. Ed. in Psych., USC. (213) 226-2114.

June 24-28—**National Society for Autistic Children—Annual Meeting.** Town and Country Hotel, San Diego. Thursday-Saturday. $30-45. Contact: Alma Spicer, 1437 Torrence St., San Diego 92103. (714) 299-3808.

July 26-27—**A Biofeedback Workshop.** UC, Santa Cruz. Saturday-Sunday. 15 hrs. $75. Contact: Darla Chadima, Cont. Ed. Specialist, Applied Sciences Bldg., UC Extension, Santa Cruz 95064. (408) 429-2971.

RADIOLOGY AND PATHOLOGY

September 27—**Current Topics in Diagnostic Radiology.** Southern California Permanente Medical Group at Marriott Hotel, Los Angeles. Saturday. Contact: Shirley Gach, So.

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KEY TO ABBREVIATIONS AND SYMBOLS

Medical Centers and CMA Contacts for Information

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103. (415) 777-2000.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Duane Dillman, PhD, Director, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 564-5911, ext. 391.

LLU: Loma Linda University
Contact: John E. Peterson, MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311.

PMC: Pacific Medical Center
Contact: Allen J. Enelow, MD, Chairman, Education Committee, Pacific Medical Center, P.O. Box 7999, San Francisco 94120. (415) 563-4321.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Neil C. Andrews, MD, Chairman, Department of Postgraduate Medicine, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, California College of Medicine, Irvine
Contact: Robert Combs, MD, Associate Dean, Continuing Medical Education, University of California, Irvine—California College of Medicine, Irvine 92664. (714) 833-5991.

UCLA: University of California, Los Angeles
Contact: Donald Brayton, MD, Director Continuing Education in Medicine and the Health Sciences. P.O. Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: Richard A. Lockwood, MD, Associate Dean for Health Manpower, 1310 Basic Sciences Building, University of California, San Diego, School of Medicine, La Jolla 92037. (714) 453-2000, ext. 1251.

UCSF: University of California, San Francisco
Contact: Malcolm S. M. Watts, MD, Associate Dean and Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-2342.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 226-2047.

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chlorzoxazone † 250 mg , acetaminophen 300 mg
*This drug has been evaluated as "probably" effective for this indication.
See brief summary of prescribing information on facing page for Indications, Contraindications, Warnings, Precautions and Adverse Reactions.
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PARAFON FORTE®tablets help relieve pain, restore mobility and stop pain-spasm feedback by providing:

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"Probably" effective as an adjunct to rest and physical therapy for the relief of discomfort associated with acute, painful musculoskeletal conditions. The mode of action of this drug has not been clearly identified, but may be related to its sedative properties. Chlorzoxazone does not directly relax tense skeletal muscles in man.

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Adverse Reactions: Occasionally, drowsiness, dizziness, lightheadedness, malaise, overstimulation or gastrointestinal disturbances may be noted; rarely, allergic-type skin rashes, petechiae, ecchymoses, angioneurotic edema or anaphylactic reactions. In rare instances, chlorzoxazone may possibly have been associated with gastrointestinal bleeding. While PARAFLEX® (chlorzoxazone) tablets and other chlorzoxazone-containing products have been suspected as being the cause of hepatic toxicity in approximately twenty-four patients, it was not possible to state that the dysfunction was or was not drug induced.
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References: 1. Batterman, R.C., and Grossman, A.J.: Fed. Proc. *14*:316, 1955. **2.** Goodman, L.S., and Gilman, A., ed.: The Pharmacological Basis of Therapeutics, ed. 4. New York, The Macmillan Company, 1970. **3.** Vickers, F.N.: Gastroint. Endosc. *14*:94, 1967. **4.** Mielke, C.H., Jr., and Britten, A.F.H.: New Engl. J. Med. *282*:1270, 1970 (Corresp.). **5.** Vernon, W.G.: Curr. Therap. Res. *14*:801, 1972. **6.** Scheiner, J.J.: Curr. Therap. Res. *14*:168, 1972. **7.** Walker, J.M.: Curr. Therap. Res. *15*:248, 1973. **8.** Data on file, McNeil Laboratories, Inc.

† U.S. Patent No. 2,895,877

McNEIL McNeil Laboratories, Inc.
Fort Washington, Pa. 19034

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Calif. Permanente Medical Group, 4900 Sunset Blvd., Los Angeles 90027. (213) 667-4241.

September 27-28—**Nuclear Medicine.** UCLA. Saturday-Sunday.

SURGERY AND ANESTHESIOLOGY

June 19-20—**Practical Management of External and Corneal Disease Problems.** USC. Thursday-Friday.

June 26-27—**Phaco-Fragmentation.** UCSF. Thursday-Friday.

June 28-30—**Phacoemulsification.** St. Mary's Hospital and Medical Center, San Francisco. Saturday-Monday. $600. Contact: St. Mary's Hospital and Medical Center, 2200 Hayes St., San Francisco 94117.

July 17-18—**Phaco-Fragmentation.** UCSF. Thursday-Friday.

July 19—**Phacoemulsification with Insertion of an Intraocular Lens.** St. Mary's Hospital and Medical Center, San Francisco. Saturday. $200. Contact: St. Mary's Hospital and Medical Center, 2200 Hayes St., San Francisco 94117.

August 6-10—**Urology—Annual Advanced Seminar.** UCLA at UC Residential Conference Center, Lake Arrowhead. Wednesday-Sunday.

August 7-8—**Phaco-Fragmentation.** UCSF. Thursday-Friday.

August 17-29—**Temporal Bone Surgical Dissection Course.** Ear Research Institute, Los Angeles. Two weeks. $1200 for otolaryngologists; $900 for residents. Contact: Jack L. Pulec, MD, Ear Research Institute, 2130 W. 3rd St., Los Angeles 90057.

September 3-December 17—**Acupuncture for Management of Musculo-Skeletal Pain.** UCLA. Wednesday evenings.

September 7-19—**Temporal Bone Surgical Dissection Course.** Ear Research Institute, Los Angeles. Two weeks. $1,200 for otolaryngologists; $900 for residents. Contact: Jack L. Pulec, MD, Ear Research Institute, 2130 W. 3rd St., Los Angeles 90057.

September 11-12—**Phaco-Fragmentation.** UCSF. Thursday-Friday.

September 18-June—**Review and Update in Surgery, Pediatrics, Ob-Gyn and Internal Medicine.** Cedars-Sinai Medical Center at Mt. Sinai Hospital, Los Angeles. Thursday evenings. Contact: Linda Alperstein, Coordinator, Cont. Med. Ed., Cedars-Sinai Medical Center, 4833 Fountain Ave., Los Angeles 90029. (213) 662-9111, ext. 206.

September 27-28—**American Society of Anesthesiologists—Regional Refresher Course.** Disneyland Hotel, Anaheim. Saturday-Sunday. 8 hrs. $50. Contact: John S. Hattox, Jr., MD, ASA, 515 Busse Highway, Park Ridge, Ill. 60068. (312) 825-5586.

September 28-October 1—**Western Neurosurgical Society.** Mauna Kea Beach Hotel, Kamuela, Hawaii. Sunday-Wednesday. Contact: John S. Tytus, MD, 1118 9th Ave., Seattle 98101. (206) 223-6641.

Orthopaedic Audio-Synopsis Foundation. A non-profit service for Orthopaedic Surgeons publishing monthly recorded teaching programs which include summaries of pertinent literature and excerpts from national and international orthopaedic meetings. Monthly c-60 cassette tapes. Annual subscription rate $75 ($37.50 for residents). Contact: A. Harris, Man. Ed., OASF, 1510 Oxley St., So. Pasadena 91030. (213) 682-1760.

OF INTEREST TO ALL PHYSICIANS

June 19-21—**Management of Medical Problems for the Family Physician.** PMC at Miyako Hotel, San Francisco. Thursday-Saturday.

July 11-20—**Associated Alumni-California College of Medicine—Annual Convention.** Hawaii. 10 days. Contact: Kay Stewart, Exec. Dir., Associated Alumni, CCM, 710 N. Euclid, Suite 210, Anaheim 92801. (714) 776-8820.

August 2—**Hypoglycemia: What It Is and Isn't.** See Medicine, August 2.

August 11-15—**Postgraduate Refresher Course—18th Annual.** USC at Sheraton-Waikiki Hotel, Honolulu. Monday-Friday.

August 14-17—**Association of Philippine Practicing Physicians In America—4th Annual Convention.** Fairmont Hotel, San Francisco. Thursday-Sunday. Contact: Lucito G. Gamboa, 35 Bradford Lane, Oak Brook, Ill. 60521. (312) 654-1126.

August 17-21—**American Society for Pharmacology and Experimental Therapeutics.** UCD. Sunday-Thursday. Contact: Dr. Keith F. Killam, Jr., Chr., Dept. of Pharmacology, UCD. (916) 752-3421.

August 20-24—**Family Practice Refresher Course—2nd Annual.** UCLA and Santa Monica Medical Center. Wednesday-Sunday.

August 24-29—**Family Practice Refresher Course—3rd Annual.** UCD. Sunday-Friday.

September 2-7—**Family Practice Review Course—6th Annual.** UCI at Newporter Inn, Newport Beach. Tuesday-Sunday.

September 3-December 17—**Acupuncture for Management of Musculo-Skeletal Pain.** See Surgery, September 3-December 17.

September 14-19—**Emergency Medical Care Review.** UCD at Pajaro Dunes. Sunday-Friday.

September 19-20—**For the Physician in Private Practice: Strategies for Managing Hypertension.** See Medicine, September 19-20.

September 22-26—**Topics in Emergency Medicine.** UCSF. Monday-Friday.

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PRECEPTORSHIPS AND TRAINEESHIPS

Training for Physicians in General Internal Medicine. LLU. Four weeks or more, by arrangement. Bedside and classroom training, practical aspects of clinical care and management. 160 hrs. Contact: John E. Peterson, MD, LLU.

Training of Physicians in Modern Concepts of Pulmonary Care. LLU. Four weeks or more, by arrangement. Diagnostic and therapeutic methods in medical chest disease, physiological methodology of modern pulmonary care programs, use of new instrumentation in the field. 160 hrs. Contact: John E. Hodgkin, MD, Chief, Section of Medical Chest Diseases, LLU.

Training for Physicians in Nephrology. LLU. Four weeks or more, by arrangement. Hemodialysis, peritoneal displays, renal biopsy, and kidney transplantation. 160 hrs. Contact: Robert E. Soderblom, MD, LLU.

Preceptorships in Cardiology. PMC. By arrangement. $200 per mo.; $500 for 3 mos. Contact: Arthur Selzer, MD, PMC.

Preceptorships in Practical Office Dermatology. PMC. Wednesdays or Fridays, 9:00 a.m.-12:00 noon, for 10 weeks. Periods begin Oct., Jan., or April. $100. Contact: Harold M. Schneidman, MD, Dept. of Dermatology, PMC.

Preceptorships in Infectious Disease. PMC. Full time for four weeks. To be arranged. $250. Contact: Rodney J. Valentine, MD, Chief, Div. of Infectious Diseases, PMC.

Preceptorships in Basic Sciences, Biochemistry and Biophysics, Dermatology, Echocardiography, International Health, Microbiology, Neurological Surgery, Obstetrics and Gynecology, Pediatrics, Pharmacology and Experimental Therapeutics, Physiology, Psychiatry, Urology. UCSF. By special arrangement.

Traineeships in Renal Dialysis. UCSF. By special arrangement.

OREGON

COUNCIL ON MEDICAL EDUCATION

THIS BULLETIN of information regarding continuing education programs and meetings of various medical organizations in Oregon is supplied by the Council on Medical Education of the Oregon Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Council on Medical Education, Oregon Medical Association, 2164 S.W. Park Place, Portland, Oregon 97205; or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

University of Oregon Medical School, Family Practice Center, 3181 S.W. Sam Jackson Park Road, Portland 97201:

Every Thursday, 8:00 a.m. to 9:00 a.m.—**Family Practice Grand Rounds.** Contact: David D. Smith, MD, Department of Family Practice, University of Oregon Medical School.

CARDIOLOGY

June 5-7—**Progress in Coronary Artery Disease and Valvular Heart Disease.** Portland. Contact: S. H. Rahimtoola, University of Oregon Medical School, 3181 S.W. Sam Jackson Park Road, Portland 97201.

FAMILY PRACTICE

Every Thursday, 8:00 a.m. to 9:00 a.m.—**Family Practice Grand Rounds.** Family Practice Center, University of Oregon Medical School, Portland. Contact: David D. Smith, MD, Department of Family Practice, University of Oregon Medical School, 3181 S.W. Sam Jackson Park Road, Portland 97201.

NEUROLOGY

June 7-8—**Oregon Neurosurgical Society Annual Meeting.** Jantzen Beach Thunderbird, Portland. Contact: Michael Mason, MD, 2525 N.W. Lovejoy, Portland 97210.

WASHINGTON, MONTANA, ALASKA and IDAHO

In order to have future activities listed here or to receive information on these and other activities, please write Ms. Joan M. Kelday, Information Specialist, Continuing Medical Education, WAMI Program, University of Washington School of Medicine, E-301, Health Sciences Building, SC-45, Seattle, Washington 98195. Phone: (206) 543-6995.

June 12-14—**Montana Academy of Family Practice Annual Meeting.** Thursday-Saturday. Farmont Hot Springs, Gregson, Montana. Contact: Francis Bertaglio, MD, 513 Main St., Deer Lodge, Montana 59722.

June 22-25—**Pacific Northwest OB-GYN Society Annual Meeting.** Sunday-Wednesday. Sun Valley, Idaho. Contact: Ms. Sylvia Gibbons, Exec. Secretary, 1220 Boren Ave., Suite 1105, Seattle 98101. (206) 682-5119.

July 30-August 1—**Idaho Medical Association Annual Meeting.** Wednesday-Friday. The Lodge, Sun Valley, Idaho. Contact: Armand L. Bird, Exec. Director, 407 W. Bannock St., Boise, Idaho 83702.

August 11-12—**Sports Medicine Workshop.** Monday-Tuesday. Graves Building, University of Washington. 13¼ hrs. $25. Contact: Richard L. Reimer, Asst. Dir. CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

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September 3-5—**Western Conference of the American Lung Associations.** Wednesday-Friday. Olympic Hotel, Seattle. Contact: Janet Chalupnik, Washington Lung Association, 216 Broadway E., Seattle 98102. (206) 329-4411.

September 8-10—**Clinical Microbiology.** Monday-Wednesday. Univ. of Wash. Health Sciences Center, Seattle. Hours and fee to be determined. Contact: Richard L. Reimer, Asst. Dir. CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Md., Seattle 98195. (206) 543-1050.

September 10-12—**Clinical Infectious Disease—American College of Physicians.** Wednesday-Friday. Olympic Hotel, Seattle. Hours and fees to be determined. Contact: Richard L. Reimer, Asst. Dir. CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

September 12-13—**American College of Physicians Regional Meeting.** Friday-Saturday. Olympic Hotel, Seattle. Hours and fees to be determined. Contact: Richard L. Reimer, Asst. Dir. CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

September 14-17—**North Pacific Pediatric Society Annual Meeting.** Sunday-Wednesday. Rosario, Orcas Island, Washington. Contact: Bernard P. DeJong, MD, Secretary, 3195 Granville St., Vancouver 9, B.C., Canada. (604) 738-2102.

September 15-16—**Liver and Cancer.** Monday-Tuesday. Univ. of Wash. Health Sciences Center, Seattle. Hours and fee to be determined. Contact: Richard L. Reimer, Asst. Dir. CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

September 17-19—**Physical Therapy Training Institute.** Wednesday-Friday. Univ. of Wash. Health Sciences Center, Seattle. Hours and fee to be determined. Contact: Richard L. Reimer, Asst. Dir. CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

September 19-22—**Washington State Medical Association Annual Meeting.** Friday-Monday. Olympic Hotel, Seattle. Contact: Harlan Knudson, Exec. Director, 444 N.E. Ravenna Blvd., Seattle 98115. (206) 523-9110.

September 26-27—**Arthritis Days '75.** Friday-Saturday. Olympic Hotel and Univ. of Wash. Health Sciences Center, Seattle. Hours and fee to be determined. Contact: Richard L. Reimer, Asst. Dir. CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

September 26-27—**Review of Basic OB-GYN.** Friday-Saturday. Virginia Mason Medical Center Auditorium, Seattle. 9 hrs. $50. Contact: Div. of CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) 223-6898.

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PHYSICIANS WANTED

SANTA BARBARA, CA. Challenging opportunities for full-time physicians in family practice, internal medicine and ob-gyn at County-operated teaching hospital. California license required. Board certification desirable. Remuneration dependent on qualifications. Contact: Edgar Rosen, MD, Medical Director, Santa Barbara General Hospital, P.O. Box 3650, Santa Barbara, CA 93105; phone (805) 967-2311.

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PATHOLOGIST—Completing University-VA residency in AP/CP August, 1975. Desires full or part-time position in S.F. Bay area or nearby. Special interest in clinical pathology. Write Box 9417, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

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THORACIC-CARDIOVASCULAR SURGEON, 40, Board eligible, born and educated in U.S., Southeastern, with open heart and coronary artery bypass experience, interested in relocating from rural Rocky Mountain area to participate in busy practice confined to specialty. California license, available July 1975. Write Box No. 9416, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

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MONTEREY, CALIFORNIA—3 offices available in new 18 suite Med.-Dental complex. Need Allergist and Oral Surgeon. Lease or limited partnership. 880 Cass, Monterey, CA 93940; (408) 649-1550.

SOUTHERN CALIFORNIA—Top location, Mesa Verde Drive Plaza, 1525 Mesa Verde Drive East, Costa Mesa, CA 92626. Please call for information (714) 545-4123.

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IDEAL SUITE. Berkeley area, 700 sq. ft. air-conditioned in modern Medical-Dental building. Prime location for family practice or Ob-Gyn. Near El Cerrito BART station. F. M. Epstein, MD, 6500 Fairmont Ave., El Cerrito, CA 94530; (415) 525-7887.

FOR RENT: The newest and largest professional building in the South San Diego community of Imperial Beach, suites available can be customized to suit tenant. This is excellent opportunity for pediatrics, gynecology, dermatology, ophthalmology, general surgery, general practice, internal medicine and psychiatry. Photos and particulars available upon request from John E. Geis, DDS, 1340 Coronado Ave., Suite 201, Imperial Beach, CA 92032; office (714) 424-3931.

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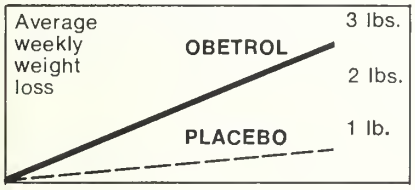
OBETROL® II

Single entity amphetamine product. Each OBETROL-10 (10 mg. tablet) contains: dextroamphetamine saccharate 2.5 mg., amphetamine aspartate 2.5 mg., dextroamphetamine sulfate 2.5 mg., amphetamine sulfate 2.5 mg. OBETROL-20 (20 mg. tablets) contain twice this potency.

Average weight loss of 2.15 lbs per week compared in clinical studies against a placebo.

CONTROLLED STUDY —
72 CASES 4 WEEKS' RESULTS



Obetrol eases the discomfort of adherence to a restricted diet in individuals who are well motivated to reduce their food intake.

Clinical studies disclose amphetamines to be the most dependable drug in a weight-reduction regimen compared to other anorexigenic agents.

Amphetamines have a significant potential for abuse. In view of their limited short-term anorectic effect and rapid development of tolerance, they should be used with extreme caution and only for limited periods of time in weight reduction programs.

Actions: Amphetamines are sympathomimetic amines with CNS stimulant activity. Peripheral actions include elevation of systolic and diastolic blood pressures and weak bronchodilator and respiratory stimulant action. The anorectic effect diminishes after a few weeks.

Indications: Exogenous obesity, as a short term (a few weeks) adjunct in a regimen of weight reduction based on caloric restriction. For patients in whom obesity is refractory to other measures.

Contraindications: Advanced arteriosclerosis, symptomatic cardiovascular disease, moderate to severe hypertension, hyperthyroidism, known hypersensitivity or idiosyncracy to the sympathomimetic amines. • Agitated states. • Patients with a history of drug abuse. • During or within 14 days following the administration of monoamine oxidase inhibitors, hypertensive crises may result.

Warnings: Tolerance to the anorectic effect usually develops within a few weeks. When this occurs, the recommended dose should not be exceeded in an attempt to increase the effect, rather, the drug should be discontinued. Amphetamines may impair the ability of the patient to engage in potentially hazardous activities such as operating machinery or driving a motor vehicle; the patient should therefore be cautioned accordingly.

Precautions: Caution is to be exercised in prescribing amphetamines for patients with even mild hypertension. Insulin requirements in diabetes mellitus may be altered in association with the use of amphetamines and the concomitant dietary regimen. Amphetamines may decrease the hypotensive effect of guanethidine. The least amount feasible should be prescribed or dispensed at one time in order to minimize the possibility of overdosage.

Adverse Reactions: *Cardiovascular:* Palpitation, tachycardia, elevation of blood pressure. Central nervous system: Overstimulation, restlessness, dizziness, insomnia, euphoria, dysphoria, tremor, headache; rarely, psychotic episodes at recommended doses. *Gastrointestinal:* Dryness of the mouth, unpleasant taste, diarrhea, other gastrointestinal disturbances. Anorexia and weight loss may occur as undesirable effects when amphetamines are used for other than the anorectic effect. *Allergic:* Urticaria. *Endocrine:* Impotence, changes in libido.

Dosage and Administration: Regardless of indication, amphetamines should be administered at the lowest effective dosage and dosage should be individually adjusted. Late evening medication should be avoided because of the resulting insomnia.

1. Narcolepsy: Usual dose 5 to 60 milligrams per day in divided doses.
2. Minimal brain dysfunction:
   a. Not recommended for children under 3 years of age.
   b. Children from 3 to 5 years of age: 2.5 milligrams daily, raised in increments of 2.5 milligrams at weekly intervals until optimal response is obtained.
   c. Children 6 years of age and older, 5 milligrams, once or twice daily, increased in increments of 5 milligrams at weekly intervals. Only in rare cases will it be necessary to exceed a total of 40 milligrams per day.
3. Obesity: Usual adult dose 5 to 30 milligrams per day in divided doses.

Overdosage: Manifestations of acute overdosage with amphetamines include restlessness, confusion, assaultiveness, hallucinations, panic states. Fatigue and depression usually follow the central stimulation. Cardiovascular effects include arrhythmias, hypertension or hypotension, and circulatory collapse. Gastrointestinal symptoms include nausea, vomiting, diarrhea, and abdominal cramps. Fatal poisoning usually terminates in convulsions and coma.

Management of acute amphetamine intoxication is largely symptomatic and includes lavage and sedation with a barbiturate. Experience with hemodialysis or peritoneal dialysis is inadequate to permit recommendations in this regard.

Availability: Supplied in bottles of 100; 500 and 1,000 tablets.

CAUTION: FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION.

January 1973

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- **less sodium**—36% less sodium than the next leading antacid.

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